BIONANOTECHNOLOGY: EMERGING APPLICATIONS OF BIONANOMATERIALS

Edited by
Ahmed Barhoum
Jaison Jeevanandam
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SECTION 1

Energy production and energy storage

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CHAPTER 1

Bionanotechnology and Bionanomaterials: Emerging Applications, Market, and Commercialization

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1. Introduction

Exhaustive, perpetual research investigations could be noted at present with respect to nanomaterials (NMs), with widespread, extensive applications stretching from biomedical engineering to electronics [1]. The augmented mechanical, optical, electrical, electronic, physicochemical, and thermal characteristics with improved surface features, and the large surface-to-volume proportion of NMs, relative to conventional resources, have gained significant attention, toward their employment in numerous solicitations [2–4]. These NMs are prepared via physical methods, such as ball milling [5], vapor deposition [6,7], laser ablation [8], and chemical synthesis methodologies, such as sol-gel [9], coprecipitation [10], polyol [11], hydrothermal [12], and solvothermal methods [13]. Even though these synthesis approaches are beneficial in fabricating smaller-sized NMs with distinct morphology, toxicity corresponding to these often surface from the hazardous chemicals incorporated during their manufacturing [14,15]. Thus, biological synthesis approaches are utilized for the fabrication of NMs to reduce their toxicity toward humans and the environment, which has led to the evolution of bionanomaterials (BNMs).

BNMs are classified into two types: naturally occurring BNMs, and NMs synthesized based on natural products or biomolecules [16]. Natural BNMs are synthesized by extracting natural materials, such as cellulose, chitin, and chitosan, from plants or living

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organisms [17]. On the other hand, the NMs, for instance, metal oxide, metal, polymeric, and carbon-based NMs, synthesized based on biomolecules and natural products, could also be perceived as BNMs [16,18,19]. These BNMs are widely utilized in numerous applications, compared with conventional NMs, due to their less/no toxicity, biocompatibility, bioavailability, and bioreactivity [20]. This chapter lays an outline of evolving applications of BNMs, including energy production, conversion, storage, and electrical and electronic application properties. In addition, the market, regulation, and commercialization of BNMs are also discussed.

2. Bionanomaterials: emerging applications

Recently, BNMs have shown enough potential with significant advantages toward numerous applications, which could be credited to their non/less toxic nature, biocompatibility, bioavailability, and potential improvement in their properties, compared with conventional NMs [18,19,21,22]. Initially, BNMs are fabricated with potential biomedical applications. However, later, they are transformed to be serviceable toward diverse sectors of applications [20]. The environmental amenability of the BNMs has made them beneficial in energy production, conversion, and storage applications [23]. Recent studies have shown that BNMs possess enhanced electrical and electronic properties, compared with conventional NMs [24]. In general, BNMs are fabricated and utilized toward a wide range of biomedical applications, including targeted drug transport [25], wound or lesion therapy [26], tissue engineering [27], medical implants [16], and biosensors [28]. The demand for environmentally friendly NMs in electronics [29], and the elevated toxicity of conventional NMs toward the environment [18,19,30,31], has made BNMs a potential substitute toward ultramodern applications in electricals and electronics, such as wearable technology [32]. In addition, these BNMs are widely employed, or under extensive study, to showcase their extraordinary potential toward energy production [33], energy conversion [34], energy storage [35], biofuel cells (BFCs) [36], biodiesel [37], and as catalysts [38]. Furthermore, these novel biogenic NMs are identified to be valuable toward air filtration [39], wastewater treatment [40], desalination [41], soil treatment [18,19,42,43], and plant protection [44]. Moreover, the BNMs are highly beneficial in agriculture, as potential pesticides [45], or as fertilizers [46], as well as in food preservation [47], and food storage [48]. Equally, BNMs also demonstrate potential benefits in oil recovery [17], textile [49], automotive [50], paper [51], and wood [52] industries via various specific applications.

3. Energy production, conversion, and storage

Energy and environment represent two key factors for the long-term survival of human beings. Power generation via the conversion of natural energy sources to electricity has been of prime interest, often manifested and realized via the incorporation of diverse,

versatile technologies. Several techniques, involving the exploitation of thermoelectric, photovoltaic, and piezoelectric materials have been developed toward power generation [53–56]. However, the advent and upsurge of nanotechnology has greatly advanced a plethora of alternative energy approaches. NMs play a key role in processing fuels from fossil fuel resources, such as natural gas, coal, and petroleum. Enlightening the efficiency of fuel production from raw materials, using nanoparticles (NPs), is more robust than many of the semiconductors used in traditional approaches [56–58]. NMs with large surface areas influence the generation of fuels via the reduced collaboration of the atoms at their surfaces, and their sites of adsorption. They are also supported in photocatalytic hydrogen and solar electricity generation, as well as the storage of electric energy with lithium-ion batteries (rechargeable) and solid-state hydrogen [54,55]. Nowadays, an efficient energy storage system (EES) constitutes a foremost and primary necessity in daily life. It can be classified by thermal (heat accumulator); mechanical (spring, pumped storage power plant, and flywheel); chemical (battery, hydrogen, methane, and redox flow battery); electrical (magnetic superconducting energy storage); and capacitors (electrical engineering). The storage of electricity is relatively complex in conventional methods. Nonetheless, advancement in nanotechnology is steadily contributing to an enhanced energy conversion, storage, and transmission [59]. Batteries are of prime importance, pertaining to their applications in electronic devices and electric vehicles. NMs are not only involved in energy production, but they also facilitate energy storage in several forms. Light-emitting NPs, such as gold or silver NPs, fluorescent NMs, and quantum dots, are generally exploited to heighten the solar cell capabilities.

3.1 Biofuel cells

BFCs represent a subcategory of fuel cells, where the catalyst at the anode and/or the cathode possesses a biological origin. BFCs are perhaps the most attractive power sources for biomedical apparatuses, which are characterized by the generation of electrical energy from chemical energy via biochemical reactions. Microbial fuel cells (MFCs), a more renowned form of BFCs, may present a potential remedy for lacking electrical infrastructure issues, and additionally within the purview of clean and renewable energy [60,61]. BFCs possess two electrodes (cathode and anode). Both or either of them represent bioelectrode/s possessing a biological enhancer or catalyst (could be either living entities or enzymes). Bioreactors are represented by organic substrates, which are directly converted into electricity using the biological system, facilitated by the involvement or presence of such catalysts [62,63]. The catalysts could be organic substrates or NMs produced by biological resources for efficient oxidation [64–66]. Organic substrates, such as organic acids, carbohydrates, wastewater, and body fluids, are used as fuels through the catabolic metabolism of the biosystem in the anode compartment. Increased electrons are then transferred to an electrode, travel to the anode, and eventually migrate via the exterior

load circuit to the cathode, with a reduced electron acceptor. The cathode receives the diffused protons with oxygen provided by air or water. BFCs are necessitated as subordinate fuels, acting as an arbitrator for the migration of electrons [67]. This electron migration procedure, from biocatalysts to the BFC anodes, could be either moderated (MET or mediated electron transfer) or direct (DET or direct electron transfer). BNMs as BFCs, including their applications, are shown in Fig. 1.1.

3.2 Bionanomaterial-based biodiesel

Nanotechnology possesses diverse applications. Particularly, enzymes that have been widely used to hydrolyze biomass for manufacturing biofuels, for instance, biogas, biodiesel from oils and fats, and ethanol [69]. In this framework, NMs replace the enzymes leading to efficient catalysis from the medium [70,71]. BFCs may be widely classified into either enzymatic fuel cells (EFCs) or MFCs, depending on the employed biocatalyst. NMs have strategic uses in biofuel production, which can be credited to their distinctive physicochemical features. Several NPs are predominantly used in biofuel production as catalytic substrates. Most significantly, the selected nanosubstrates demonstrate a large surface-to-volume proportion, quantum, and immobilized characteristics and are smaller in size. Using NMs, biofuels (biohydrogen, biogas, biodiesel, and bioethanol) are receiving more attention from researchers [72–74]. Synthesis of BNMs toward manufacturing of biodiesel is depicted in Fig. 1.2.

NMs, in the form of nanocatalysts, act as perhaps the most popular reaction enhancer or catalyst in biofuel (especially in biodiesel) production [76–78]. Biodiesel, a fatty acid methyl ester, is generally prepared by transesterification of oils, which are derived from feedstocks (plants, animals, and microorganisms). Transesterification involves the presence of both nanocatalysts and biologicals. While the reaction of nanocatalysts is similar to that of organic catalysts, it is important to assess the efficacy of the biodiesel manufacturing methodology. The mixture of feedstocks/raw materials, nanocatalysts, and alcohol is homogenized via shaker incubation to complete the reaction of transesterification [79,80]. Glycerol is a product, separated from the medium by a fractionating funnel, and purified by a rotatory evaporator functioning under reduced conditions. The residual mixture and nanocatalysts are separated by centrifugation. Based on the nature of the nanocatalyst systems, nanocatalysts have been classified into carbon scaffold-based, inorganic, magnetic, and mesoporous NMs, including immobilized NMs with biological components [81–83].

3.3 Metal/metal oxide–based nanocatalysts

Production of biodiesel has progressively involved the exploitation of solid, metal oxide, or metal-based catalysts (see Fig. 1.3). They play an important role in homogenous

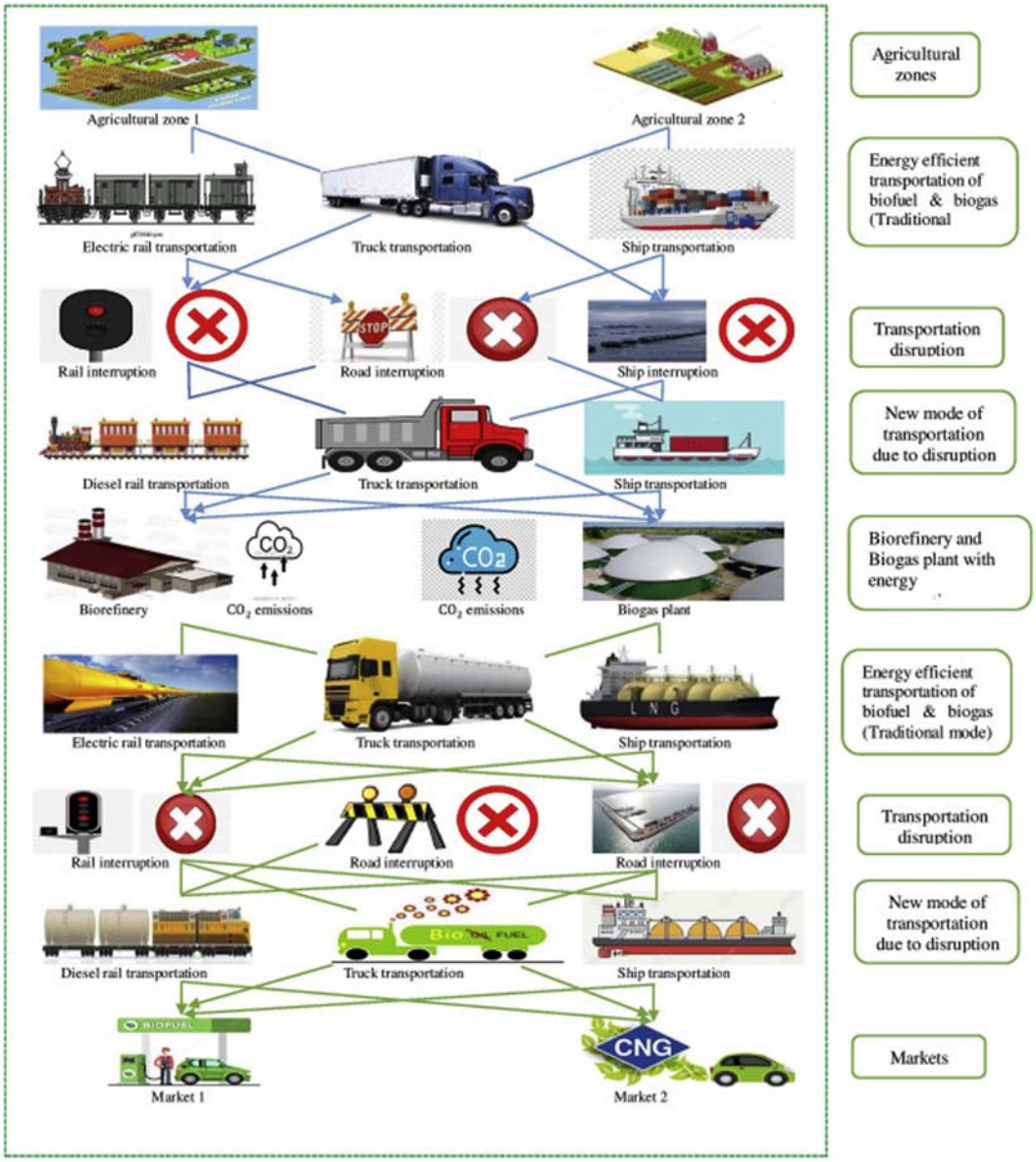

Figure 1.1

Bionanomaterials as biofuel cells and their applications [68]. *Reprinted with permission from B. Sarkar, B. Mridha, S. Pareek, M. Sarkar, L. Thangavelu, A flexible biofuel and bioenergy production system with transportation disruption under a sustainable supply chain network, J. Clean. Prod. (2021) 128079; ©Elsevier, 2021.*

Figure 1.2
Different parts of *Terminalia chebula* utilized toward the fabrication of copper oxide nanoparticles as bionanomaterials for biodiesel production [75]. *Reprinted with permission from K.V. Yatish, R.M. Prakash, C. Ningaraju, M. Sakar, R. GeethaBalakrishna, H.S. Lalithamba, Terminalia chebula as a novel green source for the synthesis of copper oxide nanoparticles and as feedstock for biodiesel production and its application on diesel engine, Energy (2021) 215119165; ©Elsevier, 2021.*

catalysis with certain limitations in the reduction. Developing newly modified metal oxide nanocatalysts toward high stability, and improved catalytic activity of NMs, including zinc oxide (ZnO) [86], magnesium oxide−calcium oxide (MgO−CaO) [87], titanium dioxide (TiO_2) [88], iron oxide (Fe_3O_4) [89], and aluminum trioxide (Al_2O_3) [90], enhances their manufacturing rate, thereby facilitating an efficient reaction catalysis process. Furthermore, mixed metal oxide NMs (alloy) show decent interactions with methanol and fatty acids. In addition to withstanding high temperatures, the tolerance of these nanocatalysts has also led to enhanced production [91,92].

3.4 Carbon-based nanocatalysts

Carbon material−based nanocatalysts, i.e., reduced graphene oxide (rGO), carbon nanotubes (CNTs), and graphene, possess noteworthy physicochemical features with

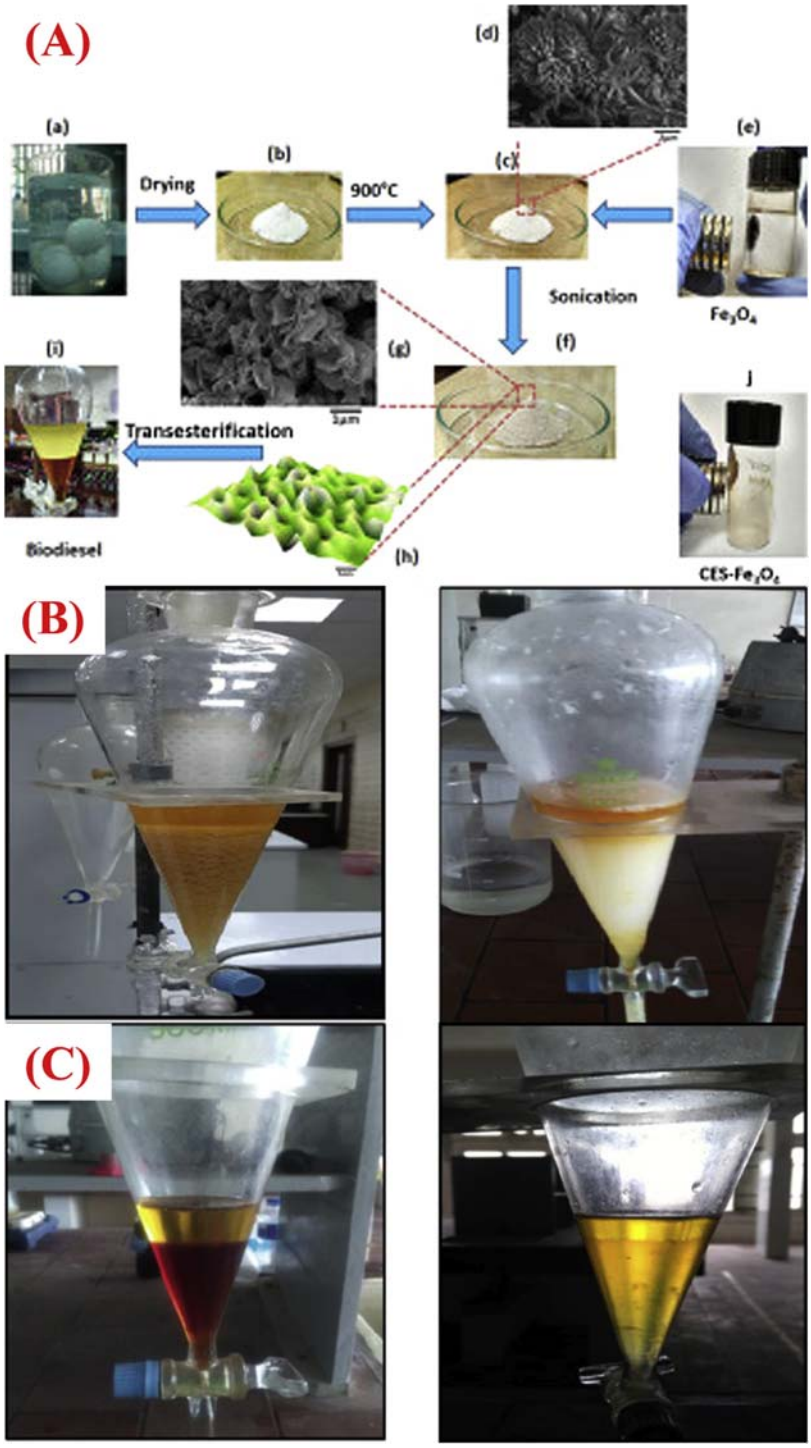

Figure 1.3
(A) Iron oxide nanoparticles [84], (B) Glycerolysis treatment for enhanced biodiesel production [85].

different morphologies [93]. Carbon materials provide numerous advantages including substantial surface area, extraordinary mechanical and thermal robustness, and functionalization procedures [94]. Graphene oxide (GO) shows a better conversion of fatty acids, which can be credited to its huge surface area and functional groups. Manufacturing of biodiesel involves a transesterification reaction (dissipated cooking oil heterogeneous catalysis) under regulated conditions [95].

3.5 Biobatteries

Recent advancements in technology have revolutionized the development of flexible and portable electronics in our daily life. Energy supplying devices, such as batteries, are an integral part among all electronic components. Batteries are anticipated to be simple and inexpensive, should provide realistic and accessible power, and must be biodegradable [96,97]. Paper-based microbial batteries have attracted attention, attributing to their sustainability, cost-effectiveness, energy accessibility, and eco-friendliness. Significant applications of biobatteries have been reported in diagnostic tools, as single-use and disposable devices. Biobatteries consist of four different functional components: (1) reservoir; (2) anode chamber; (3) ion exchange membrane; and (4) solid-state cathode or air cathode. The exploitation of easily accessible batteries, i.e., MCFs, is garnering attention, due to their surface area, porosity, bioaffinity, and conductivity [98–100]. An electroactive bacterium is a specialized subset of microbes that facilitates the anode to generate power through approachable area from bacterial extracellular electrons transfer (EET) with or without oxygen and with the anode on the exterior (via an electrical contact). The generated electrons in MFCs migrate along with the circuit (external), generate electric power, and travel to the cathode through ion exchange membranes. The microbes generally act as biocatalysts and introduce preloaded batteries before use. Several microbes are present in aquatic sources, such as the ocean, river, or pond. Some of them can generate electric current via the migration of electrons over the cellular membrane to electrodes on the exterior [101,102].

Bacterial power is generated by dropping liquid bacteria in a local setting. Preloading techniques to store cultured electroactive bacteria, as self-contained devices, are more realistic toward battery-type MFC platforms. After the completion of the manufacturing of

(A) Reprinted with permission from C. Chingakham, A. David, V. Sajith, Fe_3O_4 nanoparticles impregnated eggshell as a novel catalyst for enhanced biodiesel production. Chin. J. Chem. Eng. (2019) 27(11), 2835–2843; ©Elsevier, 2019. (B) Reprinted with permission from A.S. Elgharbawy, W.A. Sadik, O.M. Sadek, M.A. Kasaby, Glycerolysis treatment to enhance biodiesel production from low-quality feedstocks, Fuel (2021) 284118970; ©Elsevier, 2021.

the device, the electroactive bacteria are immobilized via lyophilization in the anionic chamber. Bacterial cells are utilized to seal the device to protect the bacteria from the outer contaminants. In spite of their applications, biobatteries possess some limitations in future generations in electronic devices, attributing to their short life span and toxicity. Biobatteries (around a centimeter in thickness) are widely used in thermoelectric, electrochemical, photovoltaic energy harvesters, as well as other mechanical applications, either in small scales or as lab on a chip prototype. Disposability and biodegradability are necessary features of biobatteries. BNMs toward the synthesis of biobatteries are illustrated in Fig. 1.4.

Recent advances in MFC-based biobatteries could be understood in the form of (1) flexible biobatteries, which are stand-alone, flexible energy supplying devices facilitating sustainable electronic device functions. In this regard, carbon nanofibers (CNFs) and CNTs are widely used as anode materials of MFCs to boost bacterial electron transfer from the extracellular space [104–107]. (2) Paper-based biobatteries. Cellulose fiber is a flexible substrate used in medical care, electronics, and energy. These cellulose fibers are used as paper substrates in transistors, diodes, memories, and displays. (3) Textile-based biobatteries. Textiles consist of yarns, which are the building blocks of fibers combined with human-made components, such as graphene, to synthesize the components of

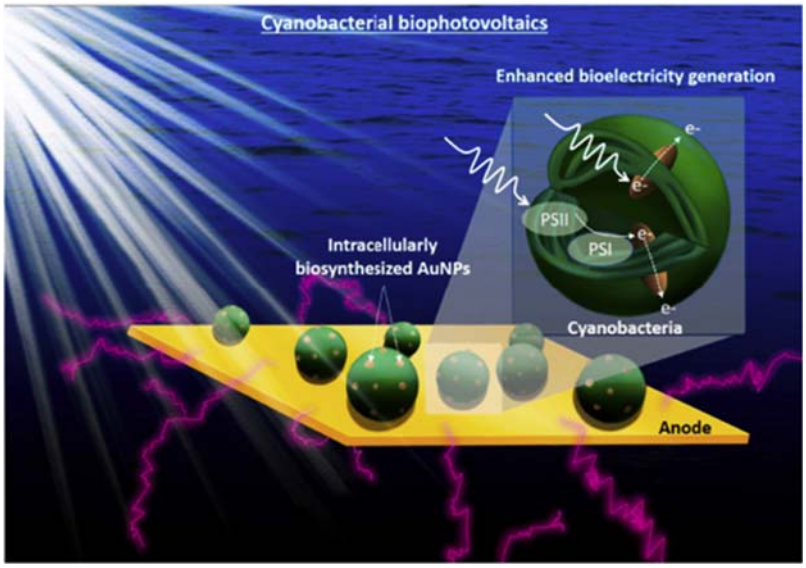

Figure 1.4

Cyanobacterial biophotovoltaics as bionanomaterials for biobattery fabrication [103]. *Reprinted with permission from L. Liu, S. Choi, Enhanced biophotoelectricity generation in cyanobacterial biophotovoltaics with intracellularly biosynthesized gold nanoparticles, J. Power Sources (2021) 506230251; ©Elsevier, 2021.*

conductive circuits, transistors, sensors, as well as energy harvesting of storage devices [108,109].

4. Environmental protection and improvements

Environmental pollution is a major global challenge affecting human life, as well as general flora and fauna. NMs are involved in a wide range of significant, real-life solicitations concerning the environment, to realize and maintain ecological sustainability. The phenomena of alleviation or elimination of ecological contaminants have particularly received considerable research focus [18,19,30,42,43]. The functional characters of NMs, such as optical, electrical, and mechanical properties, facilitate environmental remediation.

4.1 Air filtration

An ever increasing population and rapid industrialization are the root causes, which are responsible toward the fast deterioration of the quality of air in urban settlements. Pollutant-free air remains one of the most essential human assets, which is critical for their health and well-being. In this context, the evolution of technological interventions toward contaminant elimination is necessary, to substitute the traditional approaches, including separation, usage of chemical disinfectants, and adsorption, among others. However, filter materials were used to decontaminate the air inside (indoor), using nanotechnology, toward bioaerosol regulation [110,111]. Particularly, the discovery of the contaminant management technique (photocatalytic, using nano-TiO_2 material) is touted to be an innovative strategy [112]. Filtration of air, which is devoid of microbes, has garnered significant interest, facilitating original investigations in the domains of public health and quality of indoor air. Filtration is beneficial, catering to their rapid, inactive capturing of microbes, and minimizing the operational or feasible particle number, which are blown away from the filter via the air passage, affected by advanced nanotechnology. Silver (Ag) NPs have been fabricated via an aerosol procedure, which were reported to be an advantageous agent toward the filtration of microbes from air and were coated onto the exterior mask surface. Another application of Ag NPs in daily life using face masks concerns the enhanced efficacy of masks against microbial entities [113,114]. Filters made of fibers, i.e., glass fibers, spun-bonded fibers, melt-blown fibers, and nanofibers (electrospun), have been widely exploited in a plethora of air filtration gadgets. The efficacy and performance of filtration can be credited to the comparatively large pores, which are intrinsic to such filters. In filtration, nanofiber membranes are effective in resolving substrate problems using ultrafine particles with advantageous properties, including small diameters, controllable pore structures, morphology, decent internal conductivity, and a large surface area [115,116]. All these NMs would be highly

advantageous toward the alleviation of ecological pollutants via microbial degradation and air filtration.

4.2 Water treatment

Water is a precious and indispensable commodity toward the sustenance for a regular, healthy life. It contains organic and inorganic contaminants, including pesticides, dyes, pharmaceutical drugs, aromatic hydrocarbons, volatile organic compounds, and heavy metal ions [117,118]. These substances, which are harmful to living organisms, can lead to dangerous diseases. Removal of such contaminants is urgently required to save human life. Some of the advanced techniques, in this regard, include precipitation, filtration, coagulation, sedimentation, adsorption, distillation, and oxidation [119]. These techniques have been routinely used for the treatment of wastewater. However, there are some technical drawbacks, which limit the realization of their optimal potential in pollutant removal. Nowadays, nanotechnology has been extensively implemented to generate potent solutions toward the effective removal of contaminants from wastewater. The wide-scale utilization of numerous suitable agents, i.e., nanocatalysts, NP-mediated advanced filtration, nanosorbents, and biologically active NPs, among other procedures and products, has significantly resolved and refined the quality of water. NMs act as beneficial agents of adsorption, which can be credited to their surface volume, particle size, high permeability, decent electrical characteristics, and the capacity of adsorbance and contaminant binding [120]. Additionally, they demonstrate catalytic potential and high reactivity. BNM applications toward wastewater management are shown in Fig. 1.5.

4.2.1 Adsorption

Adsorption methodologies involving NMs are touted to be beneficial toward the elimination of water pollutants (both inorganic and organic). Adsorption is a surface principle, which is defined by the attachment of inorganic and organic substrates on the surface of the adsorbent via adhesion. This adhesion can be attributed to the physicochemical forces, which are predominantly manifested via the electrostatic and van der Waals interactions [122]. The hallmark of a beneficial and effective adsorbent could be associated with its noteworthy features, including resistance to mechanical forces, biocompatibility, inertness, as well as a sufficiently large adsorption capacity to assure waste elimination. These characteristics are crucial, as these can assess the material effectiveness [123,124]. The nanoadsorbents are broadly categorized as (1) carbon-based nanoadsorbents, which are CNTs, activated carbon, and graphene; (2) metal NPs, which include gold and silver [125,126]; (3) metal oxide–based nanoadsorbents, which are MgO, γ-Fe_2O_3, γ-Al_2O_3, and ZnO [127,128]; and (4) nanocomposites [129].

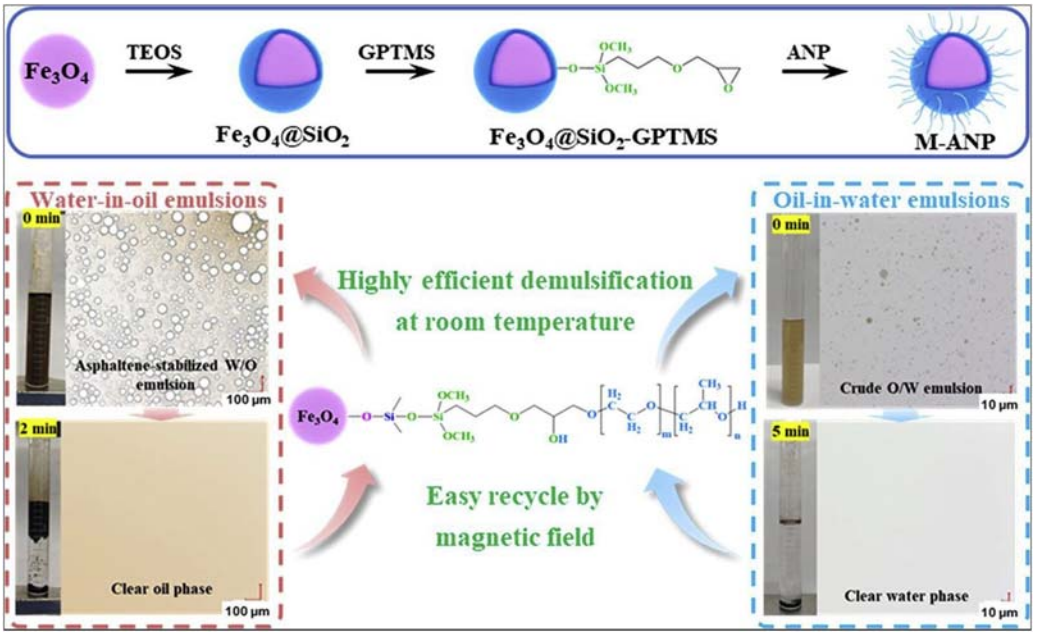

Figure 1.5

Functional magnetic bionanomaterials toward wastewater treatment [121]. *Reprinted with permission from J. Zhou, H. Sui, J. Ma, X. Li, N.H.A. Al-Shiaani, L. He, Fast demulsification of oil-water emulsions at room temperature by functionalized magnetic nanoparticles, Separ. Purif. Technol. (2021) 274118967; ©Elsevier, 2021.*

4.2.2 Nanofiltration

Filtration via the employment of membranes represents one of the critical techniques toward wastewater purification. Membranes offer a physical impediment for the pollutants, based on the size of their molecules and pores. The major advantages of using nanomembranes in wastewater treatment include high efficiency, easy operation, and low requirement for space [130,131]. In addition, the capacity of filtration could be augmented via the employment of suitable NPs. Nanofibers are widely used as nanomembrane filters for effective filtration of micron-sized particles, attributing to their permeability, large surface area, and interconnectivity.

4.2.3 Nanophotocatalysis

The photocatalytic technology garners an increased interest toward wastewater treatment, involving the principles of radiation from sunlight, and oxidizing the contaminants of wastewater. The nanophotocatalysis process may occur either homogeneously or heterogeneously [132,133]. Heterogeneous nanophotocatalysts are used in wastewater treatment, due to their scopes in the environmental application domain. Heterogeneous

photocatalysis is mostly employed with NM-assisted semiconductors that interact with either liquid or gaseous phases [134,135]. In addition, nanophotocatalysts have fascinating advantages, including stability, reusability, addictive-free, inexpensive usage of chemicals, as well as a working efficiency at a lower concentration. Recent studies have reported that TiO_2 shows an excellent photocatalytic semiconductor potential at a preindustrial scale [136–139].

4.2.4 Nanocatalysis

Several commercial and noncommercial technology developments are actively influencing our daily life. Owing to environmental concerns, NMs are being employed more routinely toward the removal of volatile organic compounds, aromatic amines, and phenol and its derivatives, among others, in wastewater treatment [140,141]. Several NMs have been used in dye removal, due to their greater degradation efficacy, and excellent physical and chemical properties. Additionally, carbon-based, metal oxide and silica-based, polymeric NMs are being extensively exploited toward the elimination of organic contaminants. BNM application as nanocatalysts toward wastewater management is depicted in Fig. 1.6.

4.2.5 Desalination

Desalination is an important alternative treatment in the collection of freshwater. NMs offer innovative scopes to advance the next generation of more effective and inexpensive reactive and nanostructured membranes facilitating water purification and desalination [143]. Of all existing desalination techniques, a membrane-based method, such as nanofiltration and reverse osmosis, is the most technologically developed and energy-efficient. NM-assisted desalination is processed by nanostructure materials, i.e., well

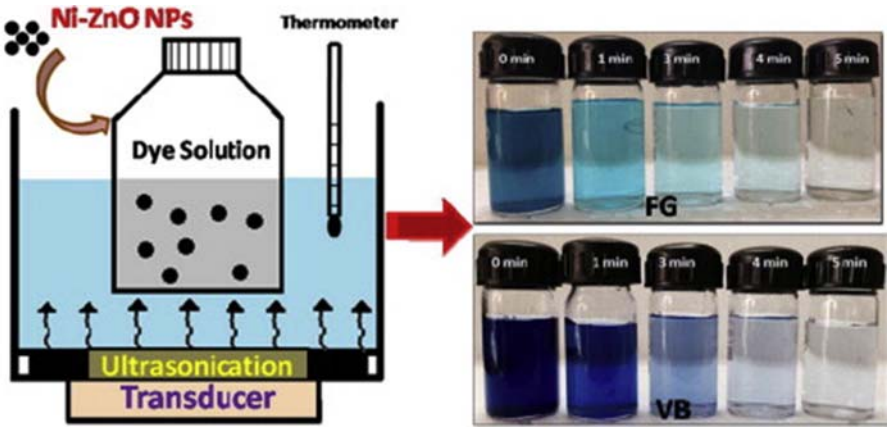

Figure 1.6

Nickel–zinc oxide nanoparticles as a potential bionanomaterial toward nanocatalysis application in wastewater treatment [142]. *Reprinted from P. Saharan, G.R. Chaudhary, S. Lata. S.K. Mehta, S. Mor, Ultra fast and effective treatment of dyes from water with the synergistic effect of Ni doped ZnO nanoparticles and ultrasonication. Ultrason. Sonochem. (2015) 22317–22325. Open Access. ©Elsevier, 2015.*

defined, size-selective NMs toward nanomembrane filtration [144]. The amalgamation of solar energy schemes with NM presents a more inexpensive, portable water manufacturing strategy, mainly attributing to their ability to speed up the condensation and evaporation rates. Various kinds of nanofluids, including numerous experimental, analytical, and numerical techniques, have been adopted to date by researchers, to advance the system efficacy [145]. For example, consider solar thermal desalination. Evaporation of water occurs as a result of the heat energy from the sun, followed by the rise of the vapor, and eventually collected from the surface of the glass as a consequence of condensation. In this process, contaminants, such as microorganisms, heavy metals, and salt get eliminated. Finally, the water that is collected is more pure relative to the cleanest rainwater [146].

4.3 Soil treatment

The constitution of soil gets altered as a consequence of the introduction of certain "xenobiotic" compounds, which ultimately adversely affect and deteriorate the quality of the soil, the phenomenon being commonly referred to as soil pollution. Majority of these contaminants are released as a consequence of everyday industrial activities, including leather, fertilizers, textile, metallurgy, and pigment synthesis, among others [147]. Diverse methodologies and techniques could be implemented, including landfilling, digging, or contaminated site capping, among others to achieve remediation of the polluted soil. These approaches include the regulated or limited exploitation of the polluted soil [148,149], which could also be subjected to a process of either excavation, encapsulation, or disposal. Organic substances such as pesticides, pharmaceutical drugs, other industrial wastages, and heavy metals (Cu, Ni, Cd, Zn, Fe, and Cr) could simultaneously contaminate the sources of soil [150].

The process of bioremediation incorporates the exploitation of living organisms to rectify polluted environments, wherein suitable interactions between the living entities and the NPs are a prerequisite. A high-magnitude retardation factor, robust adsorption, and resistant desorption indicate toward the potential of NMs to be exploited toward the elimination of inorganic and organic contaminants in sandy soil, perhaps via the implementation of in situ methodologies. For a better result, nanoremediation of soil via CNTs, metal-containing materials, semiconductor nanocrystals, and zero-valent metals could be utilized. Photocatalytic degradation by NMs is a predominant technological development to protect the soil. In this process, the decay of organic substances is facilitated by the utilization of a UV light source (sunlight), in amalgamation with the nanophotocatalysts. In soil remediation, adsorption is another important method used to remove heavy metals from contaminated soils. The elimination principle involves the migration of the heavy metal ions to adsorbent particle surface, which in turn is facilitated by the attraction forces (electrostatic) between the charged particles. The methodology is

highlighted by major primary factors, including pH, adsorbent or adsorbate charge, specific surface area, as well as the concentration of the adsorbate.

4.4 Plant protection

The characteristics of nanoscale materials could be incorporated to advance intensification remedies (agricultural), stress resistivity in plants, as well as enhancement of soil. One major challenge is to facilitate and rapidly advance plant adaptation devoid of persistent threats, including cold, water deficiency, temperature, salinity, and alkalinity, which represent delicate ecosystems as they make efforts to adjust with ecological stresses [151]. Developments in altered NMs indicate toward an advanced production of crops via nanofertilizers, where the existing conditions are detrimental toward natural plant growth. The stress corresponding to saline conditions grossly restricts the production of crops globally in the ploughed lands [152]. Noteworthy applications of NMs aimed toward the protection of plants involve the advancement of germination of seeds, and an enhancement of the fresh weight in plants, the area of leaf, and the proportion of chlorophyll. The incorporation of NMs may alleviate the risk of ailments and pests, which in turn would abate the rigorousness of productivity damages and conservational vulnerabilities. Nanoencapsulation or nanoformulation of pesticides has virtually created a revolution in the plant safeguard domain [153]. Pesticide nanoformulations incorporate extremely minor quantity of particles, which serve as pesticide active substances. Additionally, other altered or modified nanostructures also have beneficial pesticidal features. Nanoformulations could control active substance release inside the plants or the root zones, without negative effects. Several metal NPs are being used to safeguard plants from the attacks by microbes and associated ailments [154,155].

5. Biomedical applications

In the past several years, biomedical applications of BNMs have been grossly advanced, including domains such as lesion therapy, targeted drug transport, biosensors, and medical implants, among others. Major benefits of using BNMs for biomedical applications are their less toxicity along with biocompatibility, bioavailability, and bioreactivity, compared with conventional NMs [2,3,18,19].

5.1 Drug delivery

Recently, polymeric NMs are identified to be beneficial as nanomembrane entities for the controlled and targeted delivery of specific biomolecule and drugs [156,157]). It has been revealed that conventional drugs possess a lower water solubility, short plasma circulation time, poor bioavailability, rapid clearance, susceptibility to enzyme degradation, lower

uptake in cells, and a nonspecific toxicity toward normal cells and tissues. Thus, polymer-based BNMs have been reported to be highly significant in enhancing these properties and improving drug delivery efficiency [158]. Furthermore, Li et al. [159] fabricated novel nanofibers with biocompatible silk protein and chitosan as nanobiomaterials toward the encapsulation of an anticancer drug (5-fluorouracil) toward the inhibition of subconjunctival fibrosis. The results showed that it requires 25 days to 3 months for the nanofiber to release the drug, with a long-lasting inhibitory effect toward subconjunctival myofibroblasts [159]. Furthermore, Milosavljevic [160] utilized furcellaran and chitosan to synthesize a polysaccharide-based nanocapsule using an electrostatic interaction-based, layer-by-layer deposition approach. The nanocapsules were used to encapsulate doxorubicin, where its targeted delivery was achieved by modifying their surface peptide. The results emphasized that the nanocapsules are highly compatible with eukaryotic organisms, without apoptosis, erythrocyte membrane disruption, necrosis, and DNA fragmentation, toward nonmalignant cells. The study further showed that the nanocapsules, as a potential BNM, have improved the malignant cell inhibition property of anticancer drugs [160]. In addition, these BNMs are under extensive studies to be used as a specific and regulated drug transport machinery toward the management of diabetes, as well as neurodegenerative and genetic diseases [161−163].

5.2 Wound healing

Healing of wounds is another specific and general application in which BNMs are highly used, due to their enhanced biocompatibility and drug release efficacy [164,165]. Gubitosa [166] conjugated gold NPs with biomolecules from the mucus of *Helix aspersa* (snail) as a BNM to exhibit antiinflammatory and wound healing properties. The study showed that the conjugated gold NPs are nontoxic toward human keratinocytes with wound healing and antiinflammatory properties in murine macrophages with an increase in plasminogen activator (urokinase-type) receptor, which are indispensable toward the migration, attachment, and dispersal of keratinocytes. In addition, these BNMs also possess the ability to reduce the lipopolysaccharide-induced interleukin-6 and interleukin-1 beta, as well as the capability to block the synthesis of inducible nitric oxide synthase enzyme [166]. Furthermore, Hussein [167] demonstrated the fabrication of electrospun polyvinyl acid (PVA)−hyaluronic acid (HA)-L-arginine nanofibers, via electrospinning approach, as a significant BNM for enhanced wound healing applications. The outcomes demonstrated that the administration of nanocellulose has improved the mechanical properties of PVA-HA with enhanced hemocompatibility, adsorption of proteins, proliferation, and adhesive potential of human skin melanocytes after 48 h of exposure, compared with free nanocellulose fibers [167]. Furthermore, Batool et al. fabricated novel zinc oxide NPs via *Aloe barbadensis* leaf extract as a BNM toward the enhanced adsorption of carcinogenic

azo dyes (malachite green and congo red), as well as antibacterial, antifungal, and wound healing applications [168].

5.3 Tissue engineering applications

Several BNMs were also employed for the engineering of tissues, particularly hard tissues, for instance, bones [169–171]. Nezhad-Mokhtari et al. [172] demonstrated that an injectable scaffold made up of chitosan-based hydrogel with gold NPs can be beneficial toward tissue engineering applications. In this study, injectable hydrogels were incorporated with collagen and chitosan loaded with gold NPs. Additionally, aldehyde-modified nanocrystalline cellulose was employed for tissue engineering applications. The outcomes showed that the chitosan-dependent BNM acquires tissue engineering applications toward the NIH 3T3 cell line, with less cytotoxicity [172]. Moreover, Hasan et al. [173] fabricated a novel, nanobiocomposite scaffold made up of carboxymethyl cellulose, chitosan, and silver NP customized with "cellulose nanowhiskers," toward heightened tissue (bone) engineering purposes. The study emphasized that the nanobiocomposite possesses an enhanced scaffold degradation rate with enhanced antimicrobial activity, angiogenesis, vascularization, cell adhesion, and proliferation features toward MG63 cells, along with enhanced biomineralization property toward bone growth [173]. Similarly, Mansilla [174] showed that wheat germin-like protein on the surface of the chitin–chitosan matrix could be exploited toward tissue engineering claims. In this study, the wheat germin-like protease inhibitor on the biocompatible matrix can be utilized for the improvement of cell attachment ability in various mammalian cell lines. The results showed that the BNM possesses an enhanced cell adhesion property, where the protease inhibitor improved the metabolic activity and proliferation of premyoblastic C2C12 cells and the tumoral B16 cell model [174].

5.4 Medical implants

In recent times, BNMs have been utilized for the fabrication of medical implants or as a coating agent to enhance the biocompatibility of implants. López-Valverde [175] fabricated novel titanium-based dental implants that are coated with chitosan or melatonin. The BNM coated with chitosan has been proven to possess the ability to improve the bone density of jaws in Beagle dogs [175]. Furthermore, Kummala [176] reported that the implants coated with cellulose NM possess the ability to improve the adhesion and viability of human dermal fibroblast. In this study, two cellulose nanofibers (2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)-oxidized), microfibrillar cellulose, and cellulose nanocrystals were used, where the anionic cellulose nanofibers possess the ability to enhance viability with the most stable adhesion [176]. Furthermore, Jain et al. [177] fabricated a nickel-doped zinc oxide–chitin composite to be used as a potential anticorrosive coating material in zinc

alloys, toward the synthesis of the medical implant. The study showed that the BNM possesses enhanced electrochemical corrosion along with decent capacitor behaviors, including a high resistance value in a simulated body fluid [177].

5.5 Biosensors

BNMs have additionally been widely utilized toward the fabrication of biosensors aimed at detecting biological molecules and disease diagnosis [178]. Ahmadi et al. [179] prepared a paper-based and enzyme-dependent biosensor (impedimetric) with the help of electrospun cellulose acetate nanofibers (electrospun) and rGO. These novel BNMs have been proven to be beneficial for glucose identification in blood (whole) specimens, with a high sensitivity of 9.9×10^{-4}/kΩ/mM, an identification threshold of 0.1 mM, and the detection scope of 3.3−27.7 mM [179]. Likewise, Sok and Fragoso [180] fabricated a biosensor (amperometric) for tyrosinase inhibition-based glyphosate (a model herbicide), which was conjugated with tyrosinase to nanoonions (carbon-based) in a chitosan matrix on an electrode (screen-printed). The study showed that the BNM helped in the amperometric quantification of glyphosate within the proportion scope of 0.015−10 μM, with an identification threshold of 6.5 nM [180]. Similarly, Sengupta et al. [181] also demonstrated the fabrication of a carbon nitride−chitin−acetic acid hybrid modified with chemicals as a nanozyme cascade (devoid of metals, with two functionalities) of peroxidase−glucose oxidase toward the identification of glucose and peroxide via a "click-off" colorimetric approach. The study showed that the BNM possesses an enhanced ability toward the detection of glucose and peroxidase with 0.052 and 0.055 μM of peroxidase and glucose detection limits, respectively [181].

6. Agriculture and food production industries

Contemporary, rigorous farming arrangements exploit mineral and organic composts to resource critical plant nutrients. However, this tactic has also occasioned in severe depreciations of the environment and the ecosystems. Nanotechnology offers a critical part in promoting agriculture and agricultural products. Nanofertilizers embrace the prospects to counterbalance plant nourishment necessities. Additionally, it aims to convey sustainability to the crop manufacturing arrangements, without bargaining on the crop harvest. Agriculture and food industries aim toward the protection of agricultural products, including livestock and crops, for the ultimate benefits toward human sustenance [169,171,182].

6.1 Nanofertilizers

The enhancement of crop production by improving nutrient use efficacy is one of the foremost supports of sustainable agriculture and environmental health. Nanofertilizers are being prepared by encapsulating plant nutrients either on the surface or into the NMs to provide a controlled release of nutrients. These macronutrients can further be divided into either secondary or primary. Although primary macronutrients (N, P, and K) are consumed in higher amounts, secondary macronutrients (Ca, Mg, and S) are additionally, extremely crucial for plant growth. Nanofertilizers could be classified into three groups: (1) nanoformulation of macronutrients, (2) nanoformulation of micronutrients, and (3) nutrients-loaded NMs. NM uptake is facilitated via the nanopores and stomal openings [183,184], which sanction a deep penetration into the interior via plasmodesmata, eventually leading to a higher nutrient supply to plants. Such nutrients assist in the development of productivity, soil fertility, and a better agricultural product quality. The NMs possess a high reactivity and, upon their interactions with the fertilizers, facilitate an effective and augmented absorption of nutrients for the plants (see Fig. 1.7).

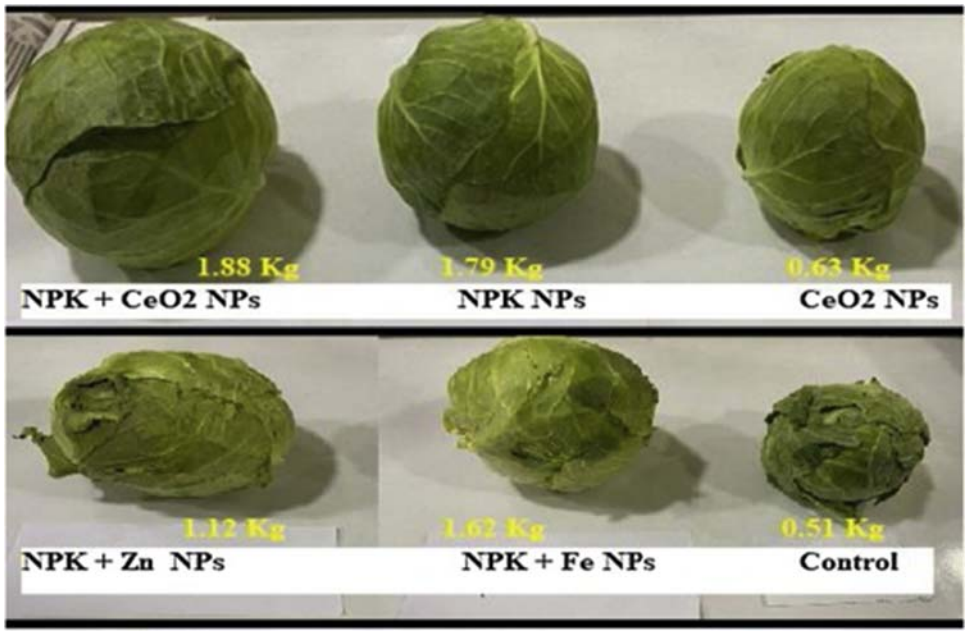

Figure 1.7

Effect of different nanoparticles as a potential bionanomaterial-based nanofertilizer for the growth of cabbage [185]. *Reproduced Reprinted with permission from M.F. Abdulhameed, A.A. Taha, R.A. Ismail, Improvement of cabbage growth and yield by nanofertilizers and nanoparticles, Environ. Nanotechnol. Monit. Manage. (2021) 15100437; ©Elsevier, 2021.*

Another important nutrient, for plant energy metabolism and protein synthesis, is nitrogen. Nitrogen-based fertilizers hold more potential to increase the production, contrary to conventional mineral urea while minimizing the disadvantages of their conventional counterparts. Nanocarriers, such as polymers (chitosan), zeolites, or clay, can coordinate with the plant's demand and release the fertilizer at a sustained rate, thereby resulting in an enhanced plant uptake, along with a justified use of nitrogen [186,187]. Characteristics, including a large surface area, and the ability to coordinate nanozeolite and nitrogen release (including their blends), have been exhaustively exploited toward designing original, next generation of nanofertilizers. Owing to the properties such as large surface area and capability to synchronize the release of nitrogen, nanozeolites, and their blends have been extensively employed for designing nanofertilizer [188].

6.2 Pesticides

Engineered NPs have potential applications in a wide range of industrial domains, such as storage, energy, storage, biomedical tools, and ecological remediation and agriculture. Prospective solicitations of nanotechnology in the domain concerning pesticides encompass an enhanced apparent solubility, and a more rapid decomposition in plant and/or soil via micro- and nanoemulsions. They are involved in the controlled release, aiding a targeted delivery of the ingredients to plants. An increasing interest in nanotechnology concerns the pesticides domain, involving the conceptualization and evolution of plat safeguard materials, i.e., nanopesticides [189]. Nanopesticides, otherwise known as agrochemicals, may incorporate either active substances, small or minor particles, or minor altered structures with beneficial pesticidal characteristics [21,22,190]. Nanoagrochemicals could be touted as specifically crucial with respect to probable ecological influences, since they only embody the deliberate diffused origin of the altered NPs in the surroundings. An illustration of the utility of polymeric NPs toward the formulation of pesticides, ultimately benefiting plant protection, is shown in Fig. 1.8.

A small number of nanopesticide products, with either a higher efficacy or a better environmental profile, are already in the market. Past reports have stressed on the enhanced efficacy of the metal NPs against a variety of plant-based adventitious agents, pests, and insects, which can be credited to their high reactive ability and smaller size, thereby influencing microbial actions [192,193]. Nanoformulation is a commonly employed pesticide formulation, due to its apparent stability, poorly soluble ingredients, or its releasing ability of the active ingredients in a targeted fashion [46,194]. Nanopesticides could be developed based on the nanoformulation methodology [195,196]. To date, several diverse kinds of nanaopesticides have been developed, including nanoemulsions, nanogels, nanocapsule formulations, metal oxide and metal NPs, and nanospheres, among others [197,198].

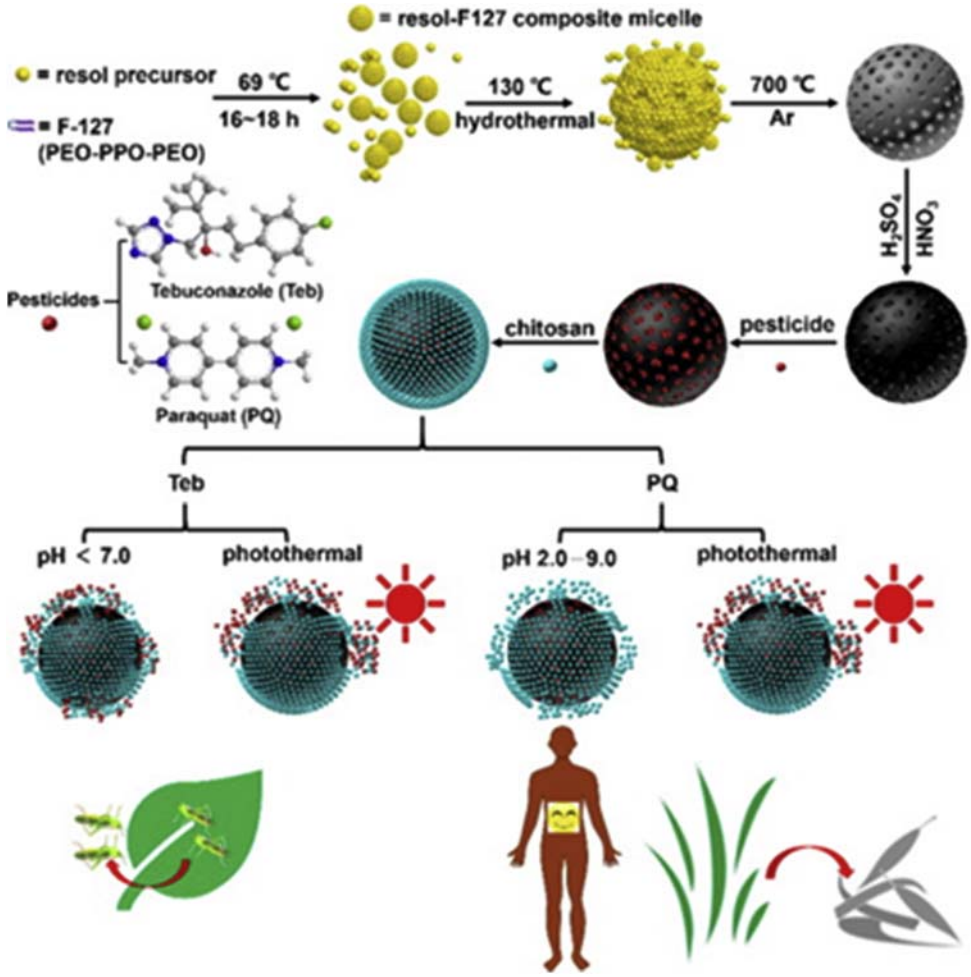

Figure 1.8

Formulation of pesticides with chitosan nanoparticles and their effects on plants to avoid the growth of pests, as well as potential damage to the crops [191]. *Reprinted with permission from J. Dong, X. Liu, Y. Chen, W. Yang, X. Du, User-safe and efficient chitosan-gated porous carbon nanopesticides and nanoherbicides. J. Colloid Interface Sci. (2021) 59420–59434; ©Elsevier, 2021.*

6.3 Food preservation

The scopes and suitability of exploitation of nanotechnology is far-reaching concerning the food industry, with conceptualization of innovation strategies toward the betterment of shelf life, quality and healthiness of food, and safety [169,171,199]. Particularly, engineered NPs enrich foods from diverse perspectives, including flavors, colors, nutrients and preservatives, rheological modifiers, and food packaging [200]. Applications of silver,

iron oxide, titanium dioxide, zinc oxide, and silicon dioxide NPs in foods uphold the most significant NP traits, which affect their processabilities in the food industry [201].

Development and utilization of food components (nanostructured) include the basic underlying claim that these convey augmented self-life, textural characteristics, nourishment value, palate, consistency, and protection against microbial infestation. NMs are used as ingredients and additives (e.g., vitamins, antimicrobials, antioxidants) in nutrients and health supplements for enhanced absorption and bioavailability [202]. The nanoparticles, such as SiO_2, TiO_2, [203,204], and amorphous silica, are used as food

Figure 1.9
Schematic showing the role of nanobiomaterials in different aspects of food sectors.

additives in food industries, and amorphous nano-silica are used as food additives and as food packaging materials in food industries. Several nanocomposites are used in food packaging applications [205]. Furthermore, polymeric NMs (biodegradable materials) have been widely used in food packaging, to extend the product shelf life, facilitating their transport [206]. It consists of nanosensors, which possess the potential to identify the spoilage or decay of foods, and the secretion of nanoantimicrobial agents to prolong their shelf life prior to the sale [207,208]. Utilities of BNMs in diverse domains of the food sector are displayed in Fig. 1.9.

6.4 Food storage

NMs have excellent antimicrobial properties, which sanction them the capability to restore food during their transport and storage. In addition, NM-based sensors are used to check storage conditions during food transport, to control the temperature, detect contamination, and regulate the food environment [209,210]. NPs (as nanoadditives) are generally used in the food or to convey original functional capabilities to the packaging unit, without altering the actual characteristics of the polymer-based package. Several metal/metal oxides have been shown to offer higher blocking ability against the UV radiation (silicon, magnesium, titanium) and as antimicrobial substances (gold, silver, copper, zinc oxide) [211−213]. Nanosensors offer distinct advantages toward the identification of trace quantities of pesticides existing in various food materials, which assists in upholding food security and safety [214,215]. These are often exploited toward the detection of pesticides as organophosphates in aquatics, fruits, and plants. The other important usage of NMs in the food industry lies from the purview of consumable coatings. Freshly chopped fruits often undergo oxidation (browning), manifested in the form of dark-colored pigments via the transformation of phenolic compounds, which could be ultimately regulated via treatments with antioxidants. NMs are directly used as antibrowning agents to prevent the oxidation of phenolic compounds. For instance, the self life of Fuji apples (as a freshly chopped product) has been shown to be advanced via the utilization of a direct packaging substance coated with nano-ZnO NPs [216]. Exploitation of inorganic NMs, such as Ag NPs, Zo, TiO_2, SiO_2, and organic NMs, such as lipid, protein, carbohydrate, and complex NPs, make a major impact in food industries.

7. Other applications

Water repellence, durability, high tensile strength, antimicrobial properties, and fire retardancy represent major concerns in textile industries. In this context, the advent and perpetual utilization of nanotechnology could be perceived as a revolution in the form of a cross-disciplinary approach.

7.1 Textiles

Textiles are one of the most heavily traded commodities in the world. With respect to distinct characteristics and functionalities of the fabrics, the inception of innovation technologies in the textile industry is worth considering. Textile technology can be improved via nanotechnology toward the design of specialized textile products that can be used for geotextiles, medical textiles, to protect from washing conditions, dyeing process, and severe environmental harms. Different nanotreatments can impart textiles with special properties. Developments in the domain of material science, in general, have led to the conceptualization of "smart clothes," with an extensively employed type of fiber type, which demonstrates a high absorbance power, softness, and an enhanced breathing ability. Applications of nanotechnology in the fabric industry also involve the wide-scale usage of quantum dots as semiconductor nanocrystals. They possess increased durability of fabrics, comfort, and hygienic with a low production cost. In the textile industry, nanotechnology involvement has been shown to convey multifunctional properties, including water repellence, breathability, wrinkle-free property, soil resistance, flame retardancy, and UV protection, among others. Nanofibers with sizes lower than 1 mm can be produced via electrospinning. Nanofibers assist toward the distribution of airflow from the exterior surface, thereby making the "slip flow" procedure critical, which can be credited to their smaller size and a large surface-to-volume proportion. Nanofibers incorporated with NMs

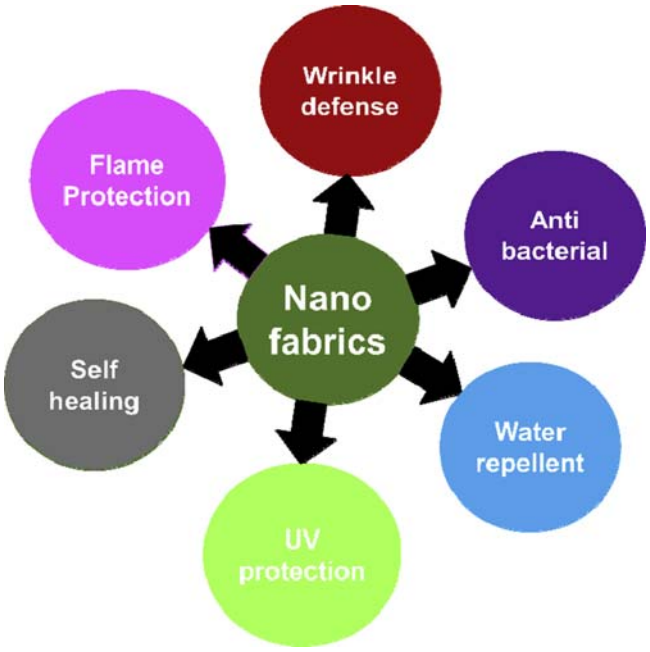

Figure 1.10
Schematic showing the potential application of bionanomaterials in the textile industry.

additionally impart self-healing [217], dirt/water repelling, and bactericidal characteristics. Nylon nanofibers represent a noteworthy fiber material coated with additional metals, which offer antibacterial properties. These nanofibers maintain high photoactivity postdye decay and recurrent cleaning. The nanocomposites of SiO_2 enhance the regulation of fragrance and the durability of the fiber. Utilities of BNMs in various associated domains in the textile industry are shown in Fig. 1.10.

A resin is commonly employed to impart crease resistance in fabric manufacturing. The limitations for applying resins include a decrease in the tensile strength and water permeability of the fiber. Researchers have developed a novel NM using SiO_2 and TiO_2 to recover the crinkle defiance of silk and cotton [218]. Many polymeric nanocomposites contain fabrics amalgamated with a "fasting matrix," showing self-healing features. In fact, within the aviation sector, the upsurge of polymeric materials with self-healing properties could be witnessed in the recent years. Nanofibers with unique mechanical, optical, and biological applications are also increasingly being applied as fillers of fibers.

7.2 Paper and wood

The inception of filter-dependent (cellulose) paper has literally interconnected nanotechnology with the paper industry. Usefulness of nanotechnology is evident via their ability to metamorphose forest products, virtually in every aspect, i.e., from original and innovative applications toward composites and paper-based materials to the manufacturing of raw materials. NM-dependent technologies are increasingly being perceived to transform the conventional wood and fiber-based products, functional lignocellulosic and wood composites, paper, and pulp. Cellulose fibers are prepared by electrospinning, including bacterial cellulose nanofibers and microfibrillated cellulose plant fibers [219]. Nanocellulose possesses crucial physical and chemical properties, morphology, surface properties, and crystalline structures. Nanocellulose replaces petroleum-based polymers toward the development of stronger paper-based and additional superior coatings. Nanotechnology also helps in the production with reduced consumption of materials [105,107,220]. The nanocoating methodology, so far, has been embraced by numerous paper mills, manufacturing papers of sufficiently high standard. In this regard, it may be noted that for the paper and pulp mills to transform as a profit generating industry, the most recent notion of "pulp mill as a biorefinery" has unearthed a handful of novel avenues [221,222]. Several NMs are made up of cellulose fiber from pulp manufacturing. These are nanocrystalline cellulose and are recyclable and renewable [223,224]. Nanotechnology applications in the paper industry are manifested chiefly in two ways: the first application concerns the creation of a new product, and enhancement of existing products; the second application concerns the way of utilization of cellulose fiber toward generation of outside industrial products [225,226]. Nanocellulose is perhaps the most

plentiful, naturally occurring polymer, which contains crystalline features that help to color films with the absence of other pigments. Nanocellulose also possesses unique mechanical properties, such as a high elastic modulus, and a greater stiffness of nearly 10-fold.

7.3 Automotive

The advancement of nanotechnology in automotive industries provides a short time consuming, a less raw source for products, and life secured techniques. Fuel efficiency in the cars, whether it is diesel, petrol, or electric, is a function of their weight. A small reduction of this weight also leads to a significantly enhanced mileage. To reduce such weights, lightweight materials provide the classical structures of the interior and the exterior, and are also comparatively stronger. Nanofabrications are responsible to produce lightweight products, which are stronger than the existing ones. Making engines, batteries, paints and coatings, and fuel cells embody some of the most important developments using NMs. It may be noted that nanotechnology is conjugated with several parts of automobiles, such as batteries, paints, tires, fuel cells, and mirrors. All vehicles are eventually subjected to utmost weather conditions, which manifest cracks, abrasions, and scratches on their surfaces. In this context, nanobased coatings have been reported to be a beneficial approach to confer the protection of the exterior surfaces [227,228]. Polymer

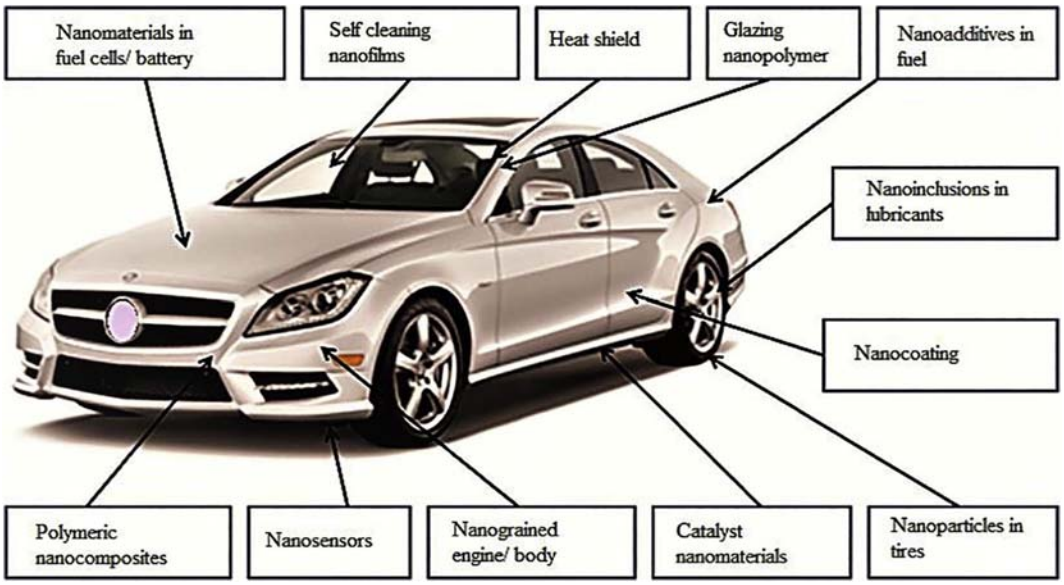

Figure 1.11

Potential applications of bionanomaterials to enhance various automotive parts [229]. *Reprinted from J. Mathew, J, Joy, S.C. George, Potential applications of nanotechnology in transportation: a review, J. King Saud Univ. Sci (2019) 31(4) 586–594. Open Access. ©Elsevier, 2019.*

NM-based coatings can advance the degree of friction and scratch protection to wear, since the coating layers can upgrade their robustness.

As is evident, NPs have been frequently used as coating materials to protect automobile body parts from scratches. They also confer a prolonged durability and improve on their appearance. Nanoadditives are also used as fuel additives to counter common wear and tear and friction of motor parts, and diminish engine emissions [230]. To date, a wide range of nanoadditives have been majorly employed to upgrade oil and fuel features, including zinc oxide, cobalt, cerium oxide, titanium, carbon, and graphene, among others. In this domain, administration of cerium oxide in blends of diesel and biodiesel represents a major research focus. This facilitates in advancing the fuel combustion to a great deal, eventually alleviating harmful emissions. Utilities of BNMs in various associated motor parts are demonstrated in Fig. 1.11.

Nowadays, electrical vehicles have garnered an increased interest, mainly to save time. Researchers and engineers are looking at the length of the battery life and their performance. This has run to the development of improved lithium batteries, with an advanced durability. One of the latest development concerns the silicon nanowires, which are tiny structures protecting lithium-rich silicon cores, and expand, shed, and absorb lithium ions [231–233]. This characteristic silicon, along with carbon shells, facilitates a more efficient energy transfer, including a lower environmental heat generation, via a lesser loss of energy [234,235]. The nanocoating of the cylinder wall, with nanocrystalline materials, can reduce abrasion and friction and facilitate low fuel consumption. The addition of nanofluids improves the coolant to enable a significant reduction of the heat transfer rate. The carrier liquid is mixed with CNTs, silica, and titanium oxide, to enhance heat reduction [236–238]. Nanotechnology also helps to improve fuel cells, which present an alternative technology to hydrocarbon fuels. The energy production via hydrocarbons involves a passage of hydrogen over a catalyst to produce hydrogen ions, which are combined with oxygen leading to energy manifestation. The role of the catalyst here is to advance the conversion of hydrogen-to-hydrogen ions using various organic or inorganic substances [239]. Researchers also developed a platinum-based catalyst that offered a large surface volume, to harvest the highest number of hydrogen ions, to produce the largest amount of energy [105–107].

In the automobile industry, tires are majorly synthesized using rubber, steel threads, and reinforcing fillers, among others. Important properties of tires are exhibited via the involvement of rubber mixtures. Smart tires embody technologically developed products that improve the performance of the existing automobile technologies. They can sense tire–load interaction parameters in a dynamic fashion, which advances the ability to conceptualize strong intelligent regulations. Additionally, self-powered or self-driven, tire-immobilized sensors can assess or interpret encrypted data (at high frequencies), to facilitate real-time regulation. In the course of vehicle movements, smart tires can

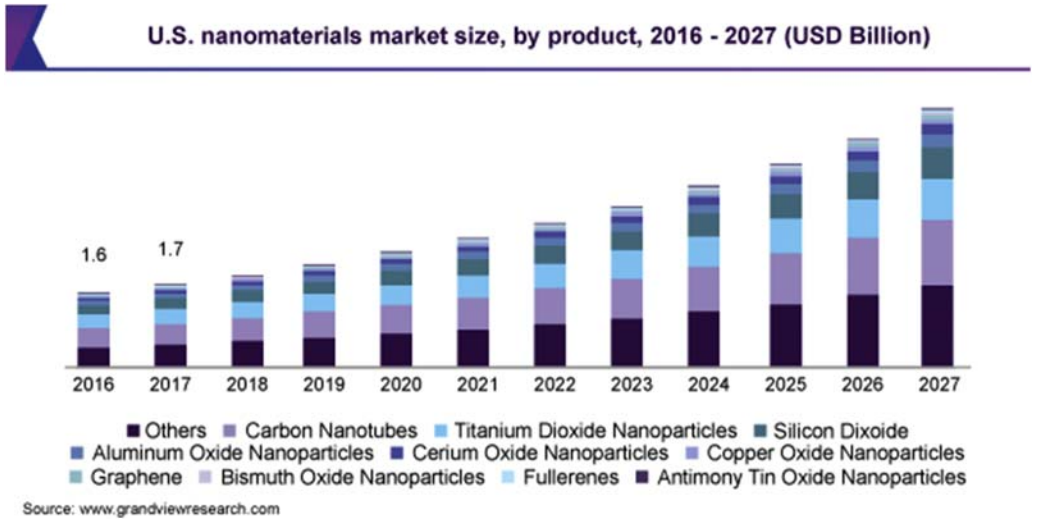

Figure 1.12
Market size of nanomaterials (by product) in the United States between 2016 and 2027 (data in billion USD). *Source: http://www.grandviewresearch.com; accessed on August 16, 2021.*

additionally measure tire–road interactions. Silver NP-based graphene sensors have been incorporated during mobile testing into the actual tires, to quantify the wavelength voltage, attributing to the tire strain produced during the movements [240,241].

8. Bionanomaterials: market growth and regulations

The NM market has been growing rapidly in the past two decades. According to an Internet-based report (http://www.grandviewresearch.com), the global market size of NMs in 2019 was USD 8500 million, which was anticipated to rise (between 2020 and 27) with a 13.1% compounded annual growth rate (CAGR), as shown in Fig. 1.12. The same report stated that CNTs possess a market share of 26.9% (2019), that titanium dioxide NPs are touted to attain a USD 4100 million market by 2027, and that the graphene NPs are anticipated to expand at a CAGR of 14.6% [242,243]. However, there is no isolated market analysis, specifically targeted toward BNMs, since their research is still in its infancy and is majorly classified under the NM category. BNMs embody a relatively new field of research, compared with conventional biomaterials, which require several regulations to avoid any detrimental effect on the environment or toward living organisms, while producing them on a large scale for commercial purposes. Each country harbors its regulatory guidelines for NMs, and separate sections have been introduced in these guidelines, specifically for BNMs, in recent times. Countries, such as China, Japan, and pharmaceutical and food sectors in Australia, as well as the pesticide sector in the United States, do not even provide definitions for engineered and BNMs in their regulatory

guidelines, which makes it difficult to propose new BNMs toward commercial applications. Furthermore, it can be noted that compulsory labeling schemes of engineered or BNMs are not required in commercial products, in any country, except in the cosmetic sector of the European Union. Thus, it is evident that only a few sectors in the United States and the European Union provide specific standardized guidance toward the toxicity tests, characterizations, risk assessments, and applications of commercial products with BNMs [244]. Recently, government organizations, such as the Royal Academy of Engineering, the United States environmental protection agency, the Royal Society, Scientific committee of the European commission, and nongovernmental organizations, including "Friends of the Earth" and "Xpert Arena," are actively involved in the drafting and implementation of regulatory measures related to the prospective risk and toxicity evaluation of BNMs [245]. However, lack of a proper definition for BNMs, such as characteristic properties or insolubility, along with unsolved analytical challenges, makes it difficult to classify BNMs under any regulatory requirements [246]. Hence, the regulations in BNM production toward environmental protection and human health may face a path of several legal uncertainties, which may be avoided by drafting a proper definition for BNMs in the future.

9. Commercialization of bionanomaterials

It has been revealed in recent reports that NMs, such as calcium and aluminum oxide, carbon-based NMs (CNTs, fullerenes, graphite, graphene), clay, ceramics, cobalt, gold, copper, iron, magnesium, lead, nitrocellulose, platinum, polymer, quantum dots, silicon-based, silver, zeolite, tungsten disulfide, zirconia, and zinc oxide, have found wide-scale commercial applications in diverse domains [247]. However, the production cost of NMs is also higher, and hence, they are expensive in the current market, compared with conventional materials [6,7]. The high expense associated with NMs is a major hurdle that stands in the way of their optimal exploitation in commercial-scale applications. Recently, cellulose-based BNMs are being touted as prospective candidates toward commercial applications. Ong et al. [248] have found the security of innovative cellulose NMs (biologically derived) toward commercialization. In this study, lignin-coated cellulose nanofibrils and nanocrystals were synthesized, and a security assessment protocol was developed, depending on the risk evaluation (nano−life cycle) and counsel of numerous regulatory bodies. The study showed that cellulose-based BNMs were nontoxic, compared with conventional cellulose, which can undeniably be exploited toward commercial applications [248]. However, several aspects need to be considered toward the commercialization of BNMs in the future, especially designing a novel synthesis approach to reduce their production costs.

10. Conclusions

In this chapter, various emerging applications of BNMs have been discussed, which will be beneficial for the current researchers. Furthermore, the market, regulation, and commercialization of BNMs have also been discussed, which will be useful to improve their commercial applications in the future. The novel synthesis approaches, which are being developed in recent times, show promising aspects to improve the commercial aspects of BNMs, with enhanced properties and applications at a reduced cost.

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CHAPTER 2

Smart bionanomaterials for the removal of contaminants from wastewater

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1. Introduction

Water is an important and inevitable resource essential for the survival of all life forms. However, only 1% of the water in the globe is fit for human consumption [1]. Supplementation of pure and affordable water remains a conspicuous task of the century [2]. In recent years, water pollution has become a global crisis due to the rapid development of industrialization and urbanization [3]. Plunging of pollutants intensively or accidentally onto the environment results in severe ecological perturbations with global ramifications. Contamination of water sources by industrial effluents is the major factor that limits the accessibility and quality of the water supply chain.

Worldwide, millions of tons of toxic industrial wastes are dumped into the water resources every year [4]. By 2050, it is estimated that industrial water consumption and pollution will escalate up to 400% globally [5]. Therefore, international environmental protection agencies such as the United States Environmental Protection Agencies (US EPA), American Public Health Association (APHA), and World Health Organization (WHO) have framed regulatory limits for industries to minimize the load of pollutants. To date, more than 700 organic and inorganic pollutants such as heavy metals, dyes, pharmaceuticals, pesticides, and hydrocarbons are reported to be toxic to the environment and humans [6]. Continuous discharge of industrial effluents into water resources results in a negative impact on humans and other organisms (Table 2.1). Uptake of pollutant-contaminated water results in mutagenic and genotoxic diseases in humans [7].

Numerous physical and chemical methods such as coagulation, filtration, electrochemical treatment, adsorption, membrane filtration, precipitation, pH neutralization, oxidation, and

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Table 2.1: General environmental standards and permissible limits of pollutants [8,9].

Types	Contaminants	Permissible standards mg/L	
		USEPA	WHO
Metals	Chromium	0.1	0.05
	Copper	1.3	1.0
	Arsenic	0.05	0.05
	Cadmium	0.005	0.003
	Mercury	0.002	0.001
	Nickel	—	0.07
	Lead	—	0.01
	Zinc	—	5.0
	Fluoride	4.0	1.5
	Selenium	0.05	0.04
Organic chemicals	Pentachlorophenol	0.001	0.009
	2,4,6-Trichlorophenol	—	0.2
	2,4-Dichlorophenol	—	0.3
	2-Chlorophenol	—	0.1
	Dichlorodiphenyltrichloroethane (DDT)	—	0.001
	Carbofuran	0.04	0.007
	Aldrin	—	0.003
	Dieldrin	—	0.002

reduction are in practice for a long time. However, these methods have their drawbacks and fail to eliminate the pollutants from the wastewater. Furthermore, the removal of certain pollutants is still a challenging task because of poor solubility and recalcitrant nature (Table 2.2).

In this regard, the application of nanotechnology is an ideal and viable option in the effective treatment of pollutants. In recent years, nanotechnology has transpired as efficient and versatile technology in scientific research. Further nanomaterials offer a wide scope in the development of novel materials with versatile and commercial applications in industrial research. Bionanomaterials are at the leading edge of the rapidly developing field of nanotechnology. The unique physicochemical properties of bionanomaterials such as size, high surface area to volume ratio, quantum nature, and less toxicity enable them for application in diverse fields such as medicine, biology, and chemical sciences including energy and environmental applications. These unique characteristic features of bionanomaterials had transformed them into eco-friendly materials in nanomaterials research. A wide range of methods are available for the fabrication of smart nanomaterials (Fig. 2.1).

Bionanomaterials have attracted considerable attention in wastewater treatment due to their renewable nature, better absorption efficiency, and low-cost production. Especially,

Table 2.2: Sources and types of environmental pollutants.

	Contaminants	Sources	References
Inorganic pollutants	Chromium (Cr)	Electroplating industries and tannery effluents	[10–12]
	Nickel (Ni)	Electroplating, mining, paintings, pesticide, fertilizer, and battery industries	[13–15]
	Copper (Cu)	Electroplating and electronic industry	[16,17]
	Arsenic (As)	Metal plating, welding alloys, batteries, and paint pigments	[18–20]
	Cadmium (Cd)	Metal plating, welding alloys, batteries, and paint pigments	[21,22]
	Mercury (Hg)	Cement factories, mining, textiles, tanneries, and fertilizer industries	[23,24]
	Lead (Pb)	Manufacturing of batteries, paint and plastic industries, also form urban waste	[25,26]
	Radionuclides	Nuclear power plants	[27–29]
Organic pollutants	**Phenolic compounds**		
	Phenol, 2-chlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol, pentachlorophenol, 2,4-dinitrophenol	Herbicides, pesticides, pharmaceuticals, and paper mills	[27,28]
	Dyes		
	Azo dyes, anthraquinone, triarylmethane, phthalocyanine	Textile, leather, and paint industries	[29–31]
	Pharmaceutically active compounds		
	Erythromycin, estrone, diclofenac, citalopram, carbamazepine	Manufacturers of pharmaceutical chemicals, discharge from household wastewaters, and expired drugs	[32,33]
	Personal care products (PPCPs)		
	Triclosan, galaxolide, triclocarban, benzotriazole, isophorone	Soaps, lotion, UV blockers, domestic wastewaters	[34,35]

bionanomaterials tend to have a specific focus on the treatment of industrial wastewater due to their environmentally benign nature. To date, bionanomaterial-dependent technologies are considered a viable alternative to traditional wastewater treatment techniques. Fig. 2.2 highlights the application of bionanomaterials in treating environmental contaminants. Furthermore, nanoremediation using nanoscale biomaterials

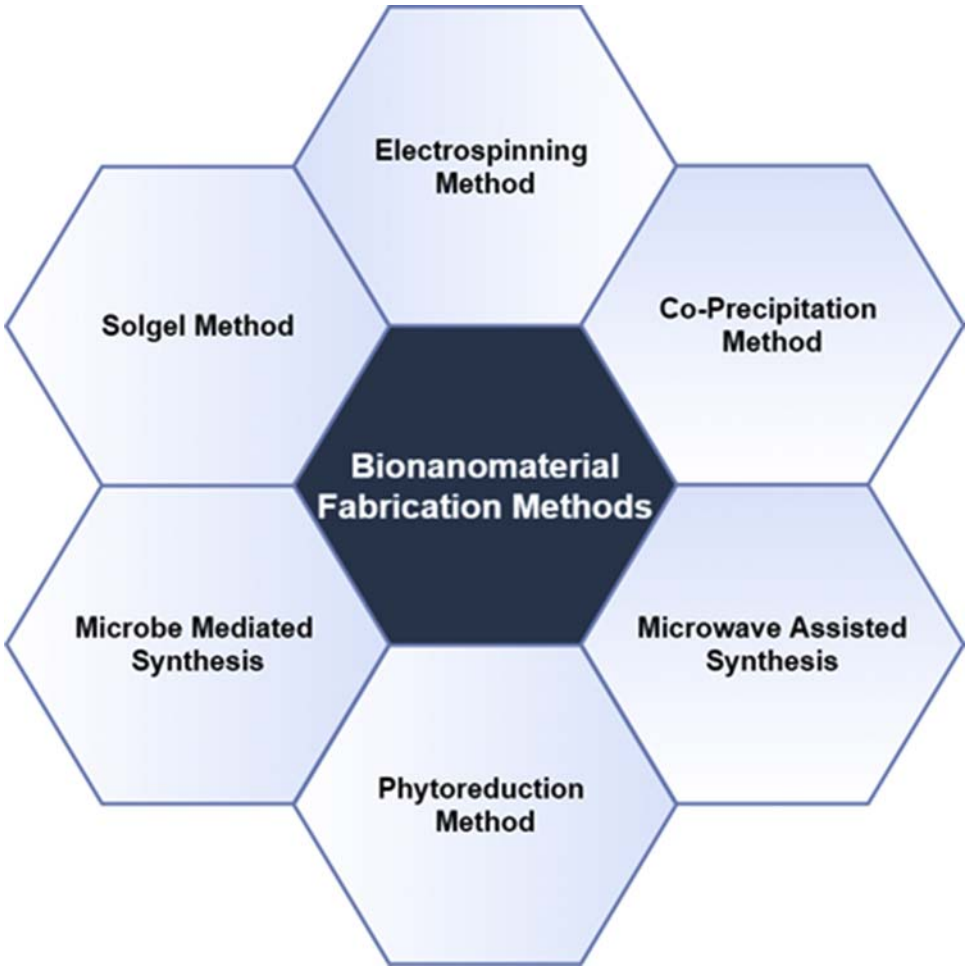

Figure 2.1
Fabrication methods for the synthesis of bionanomaterials.

offers a potential solution for environmental cleanup by playing a significant role in pollution prevention, detection, monitoring, and remediation. Nanoremediation implicates the application of reactive functional bionanomaterials for the transformation and detoxification of hazardous materials. Nanoremediation relies on the peculiar properties of nanoscale biomaterials such as nanofibers, nanoadsorbents, bionanocomposites, nanopolymers, and nanobiosorbents. Therefore, this chapter discusses the features, applications, and limitations of different bionanomaterials and their role in wastewater treatment.

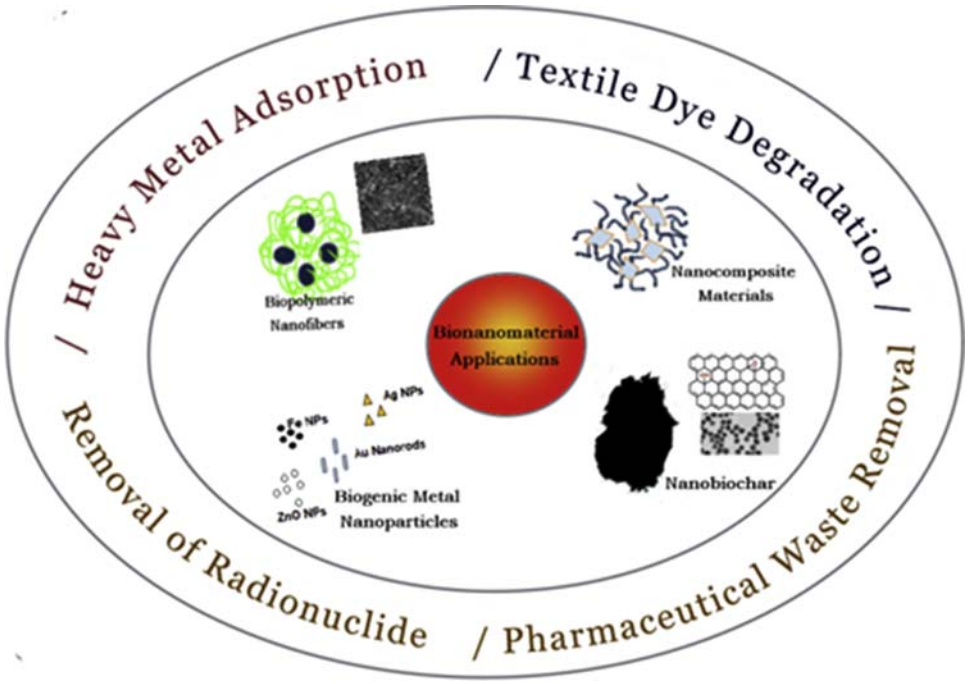

Figure 2.2
Application of bionanomaterials in the treatment of diverse environmental pollutants.

2. Biopolymer nanofibers in the treatment of wastewater

Biopolymers are fascinating materials derived from natural sources, which are biocompatible and zero toxic. Different forms of biopolymer nanomaterials such as nanofibers, nanocomposites, nanofillers, and nanomembranes are found to possess tremendous applications in the environmental remediation of pollutants [36,37]. Electrospun nanofibers fabricated by an electrospinning process are gaining considerable attention in recent decades [38]. Generally, nanofibers are defined as polymeric materials with diameters less than 100 nm. The precise nanofiber size imparts small pore cavities between the adjacent fibers and confers high specific area, porosity, affinity, absorption efficiency, and insulation capacity.

Electrospun nanofibers exhibit high porosity (80%). However, the conventional membrane filters have a 0.5%−35% of porous nature. This unique improved interconnected pore structure and high porosity are the key features responsible for the trapping of the contaminants from the wastewater [39]. Zheng et al. [40] highlighted that biopolymer-based nanofibers are considered superior materials for the complete elimination of toxic dyes from wastewater. Different biopolymers such as cellulose, chitosan, keratin, and hydroxyapatite are documented for their potential in the elimination of pollutants such as

heavy metals, dyes, pharmaceutics, and phenols [41–43]. Reactive functional groups present in the biopolymer nanofibers such as carboxyl, hydroxyl, carbonyl, amines are responsible for the chelation of metal ions from the wastewater via electrostatic interactions [44]. Of the different biopolymers, cellulose and chitosan were found to be efficient biomaterials in all aspects of availability, efficiency, versatility in modifications, and also in the economic point of view. Cellulose is the most explored biopolymer material for a long time. Recently, nanoforms of cellulose polymers, such as nanocellulose, cellulose acetate, and cellulose acetate phthalate, are tested in several industrial applications due to their inherent properties.

Surface modification of nanofibers with active functional groups renders adsorption of pollutants from wastewater [45]. Abu-Danso et al. [46] fabricated cellulose nanofiber tethered with sulfur for the effective removal of Pb (II) and Cd (II) ions from industrial wastewater. The finding of the study demonstrates the additive effect of surface-modified cellulose nanofibers with metal removal potential. Hydroxyapatite-incorporated cellulose acetate nanofiber was fabricated by electrospinning technique [47]. The results of the study highlighted that ion exchange surface complexation of the bionanomaterials is responsible for the removal of heavy metals Fe(III) and Pb(II). Similarly, Aliabadi et al. [48] investigated the removal of Co and Ni ions with electrospun hydroxyapatite/chitosan nanofiber. Zhou et al. [49] prepared cellulose acetate–blended silk fibroin electrospun nanofibers for heavy metal removal. The findings of the study insisted that the presence of high polar groups in the nanofiber and the large surface area of the fabricated nanofiber favored the efficient removal of metal ions. Yang et al. [50] developed amino-functionalized chitosan nanofiber by grafting polyethyleneimine and poly(glycidyl methacrylate) for chromium removal. The grafted nanofiber exhibited good stability and reproducibility.

Biopolymers from microbial sources such as polyhydroxybutyrate and alginate-mediated removal of dyes from wastewater are a hot topic of research in recent times. Alginate nanofibers are extensively studied for their diverse applications in scientific research due to their water-soluble nature and versatile physical and chemical properties. The presence of negatively charged carboxylate group in the alginate structure imparts high selectivity and adsorption property over several organic and inorganic pollutants [51]. Guo et al. [52] evaluated the brilliant blue dye filtration property of the electrospun polyhydroxybutyrate/calcium alginate/carbon nanotube-based composite nanofiber at low pressure and high flow rate conditions. Simultaneously, calcium alginate–coated electrospun polyhydroxybutyrate/carbon nanotube nanofiber was fabricated by Zhijang et al. [53]. The results of the findings were able to filter multiple dyes such as Brilliant blue, Direct orange S, Procion Red MX-5B, Hydrazine yellow, and stilbene yellow efficiently.

In addition to the naturally available biopolymers, chemically synthesized biodegradable polymers such as polyvinyl alcohol (PVA), polylactic acid (PLA), and polyaniline (PANI)

are also gaining significant attention in the removal of environmental pollutants. Karim et al. [54] fabricated chitosan/PVA-blended composite nanofiber as a potent nanobiomaterial for the specific removal of Pb (II) and Cd (II) heavy metals from wastewater. The dye removal efficiency of PVA/chitosan/Fe(III) nanocomposite fiber was investigated by Ghourbanpour et al. [55]. PVA/chitosan/Fe (III) actively adsorbed the methyl orange in both acidic and alkaline conditions with the maximum adsorption capability of 810.4 mg/g. The adsorption efficiency remains unaltered even after five times. Kebede et al. [56] investigated the adsorption efficiency of PVA-blended moringa seed protein nanofiber for the removal of pharmaceutical contaminant carbamazepine. Maximum adsorption efficiency of 95% was obtained at pH 5.5 with a concentration of 0.25 mg/L.

3. Bioinspired nanocomposite materials in the removal of environmental contaminants

Composite materials are generally made of different molecules such as polymers, metals, and ceramics. Depending upon the type of molecule and their combination, properties and applications of composite materials differ. Nanocomposites are defined as materials in which one part of the component is nanosize in nature [57]. Nanocomposites offer potential benefits than other nanomaterial types from the fabrication and economic point of view. Recent advancements in the field of bionanotechnology have shifted the path of nanocomposite materials toward the usage of biomaterials for the development of green bionanocomposites in environmental pollutant removal [58]. Bionanocomposite materials are receiving immense interest in multiple scientific disciplines due to their versatile properties such as biodegradability, stability, solvent resistance, and processability. Especially biopolymer-based nanocomposites confer a unique research space for the development of eco-friendly nanoscale materials with industrial applications. Polymer nanocomposites are complexed with organic and inorganic fillers within the polymer matrix. The molecular interaction between the fillers influences the physical and chemical properties of the nanocomposites [59].

Sadeghi-Kiakhani et al. [60] reported that chitosan-based nanocomposites can efficiently remove anionic dye from textile industry wastewater. Sankararamakrishanan et al. [61] developed an iron-doped cellulose nanofiber composite from sugarcane bagasse-based agrowaste. The fabricated bionanocomposite was stable and biodegradable. The composite material was reported to be a promising material for the removal of organic dye from industrial effluents. Moussout et al. [62] explored the possible chromium removal efficiency of chitosan/bentonite nanocomposite from tannery wastewater. Currently, biopolymer-supported binary metal oxide nanobiocomposites are reported to have extreme photocatalytic activity in wastewater remediation. Nisha et al. [63] fabricated

chitosan-modified BiO_3−CeO_2 nanocomposite by a coprecipitation method for the treatment of Acid Blue 113 dye in the presence of sunlight. Dual biopolymer-based alginate/pectin nanocomposite was fabricated by Mirza and Ahamed [64] for the effective removal of crystal violet dye. The nanocomposite was amorphous and highly porous. In addition, the nanocomposite exhibited potent regenerative property, even after the third cycle with constant absorptive behavior. Furthermore, the results of the study highlighted the compatibility of the biopolymers and environmental factors such as pH, contact time, temperature, and dosage are the prominent factors responsible for the adsorptive potential. Similarly, Zamel et al. [65] suggested cellulose acetate and polyethylene oxide (CA/PEO) as exclusive materials for immobilizing *Bacillus paramycoides* isolated from industrial effluent for the biodegradation of pollutants.

Green synthesis of novel and eco-friendly xanthan gum and methionine-bentonite nanofiller-blended bionanocomposite was carried out by Ahamed and Mirza [66] for the elimination of toxic congo red dye. A novel pine magnetite/pine biomass blended nanocomposite was developed by Mtshatsheni et al. [67]. The bionanocomposite was synthesized by the coprecipitation method in alkaline conditions in an inert environment for the removal of methylene blue. The magnetite pine nanocomposite exhibited high adsorption capacity with a combined magnetic separation approach.

Furthermore, microbial-mediated synthesis of silver bionanocomposite material for the degradation of the organic pollutant 4-nitrophenol was assessed by Narayanan and Sakthivel [68]. The synthesized nanocomposite material was reported as an eco-friendly approach for the complete removal of the pollutant. Simultaneous adsorption and degradation of organic dye using iron-based core−shell nanocomposite were designed by Fan et al. [69]. Furthermore, in the novel approach, the fabricated nanocomposite was surface-engineered to bacterial cells to enhance the elimination of toxic dyes from wastewater in a short time. Behl et al. [70] fabricated an innovative and sustainable microalga coupled graphene oxide−based bionanocomposite for the decolorization of textile dye wastewater. The formulated bionanomaterial removed 90% of the dye components under sunlight with subsequent biodiesel production. Banerjee et al. [71] reported the immobilization of bacterial consortium on polyacrylic acid−linked graphene oxide nanocomposites. The bacteria-immobilized graphene oxide nanocomposite was assessed for its ability in removing the dye components present in the textile effluents. The removal efficiency of the nanocomposite material was reported to be 99% with a contact time of 12 h.

4. Photocatalytic applications of bionanomaterials in pollution abetment

Nanoparticle-mediated treatment of wastewater has escalated as a prominent technology in the industrial sector in recent times. The advanced oxidation process, such as Fenton

oxidation, electrochemical oxidation, photocatalytic oxidation, and ozonation, is considered to be a viable alternative process for the complete elimination of environmental pollutants [72]. Several studies had highlighted the role of photocatalysis as a convenient and cost-effective approach in the degradation of pollutants and wastewater remediation [73,74]. However, the choice of the light source is the critical factor that limits the wide commercial applications. Therefore, different attempts are in progress by replacing visible light/sunlight for the photocatalytic degradation of hazardous pollutants. In addition to the light source, the type of catalyst used for the photocatalytic activity determines the degradation potential of the pollutants. Semiconductor materials SnO_2, ZnS, and TiO_2 are reported to act as effective photocatalysts for reactions. These photocatalysts absorb energy from the light source and get excited and finally generate hydroxyl (OH) radicals and degrade the pollutants. The hydroxyl radical acts on the contaminants, undergoes complete mineralization, and reduces the toxicity [75]. Furthermore, different factors such as pH, photocatalyst stability, and catalyst dosage were found to influence the rate of degradation [72,76].

Immense effort has been put forward in the development of novel biocatalytic systems that efficiently harvest UV and visible lights for pollutant degradation. Biofabricated nanomaterials are receiving huge interest in wastewater remediation due to their unique properties such as compressibility, short intraparticle diffusion distance, outstanding stability, reusability, and low toxicity [77]. Krishnamurthy et al. [78] demonstrated the photocatalytic degradation of methylene blue dye–containing wastewater using *Yucca filamentosa* leaf extract–mediated synthesis of gold nanosheets. Surface-modified biogenic silica-based polyacrylonitrile composite nanofiber was fabricated for the photocatalytic degradation of malachite green dye [79]. The influence of pH, dye concentration, and the exposure time were assessed for photocatalytic degradation under visible light illumination. Maximum degradation efficiency (95%) was observed at pH 7 in less than 10 min.

Noman et al. [80] investigated the combined photocatalytic dye detoxification effect of textile effluents in presence of biofabricated copper nanoparticles. Supplementation of biogenic nanoparticles alters the physicochemical status of the textile effluent and subsequent azo dye degradation. Mohanta and Ahmaruzzaman [81] developed an integrated green synthesized SnO_2 quantum dots encapsulated carbon nanoflakes for the removal of Bisphenol-A. The findings of the study insisted that coupled adsorption/photodegradation process conferred improved photocatalytic behavior due to $\pi-\pi$ interaction and electron sinking ability of the adsorbent.

Gavade et al. [82] evaluated the photocatalytic efficiency of green-synthesized gold-anchored ZnO nanorods for the degradation of industrial dye effluent under sunlight. The study demonstrated excellent photocatalytic degradation of dye due to the extended

absorbance of visible light. Furthermore, toxicity assessment studies of the treated effluents exhibited very low toxicity in the model organism Nile tilapia *Oreochromis niloticus*. Biofabrication of mesoporous nonmetallic element−doped TiO_2 photocatalyst through egg white protein was carried out by Kadam et al. [83]. The study addressed the application of simulated solar radiation for the degradation of dye rhodamine B. The egg white protein−fabricated TiO_2 nanoparticle exhibited excellent biodegradability of the pollutant due to the synergetic effect of nonmetal element doping. Heitmann et al. [84] investigated the application of microbial biopolymer polyhydroxybutyrate (PHB) nanocomposite for the degradation of methylene blue in the presence of UV radiation. In situ generation of free radicals generated from PHB biopolymer is responsible for the degradation of methylene blue in the presence of UV radiation. Furthermore, the study sheds light on the degradation of pollutants in the absence of metallic semiconductor materials.

ZnO nanoparticle was synthesized using the pulp of Indian bael for the treatment of methylene blue in textile industry wastewater [85]. Maximum degradation of the dye was observed at pH 9 at 90 min duration. The alkaline conditions elevate the formation of more free hydroxyl radicals, which eventually activate the photocatalytic activity in the presence of UV light. El-Gendy et al. [86] investigated the photocatalytic activity of ZnO/FAP nanocomposites for the removal of chlorophenols. The incorporation of ZnO/FAP nanocomposites showed excellent photocatalytic and degradation activity. Photocatalytic activity of the gold nanoparticles (AuNPs) for the degradation of phenolic azo dye was assessed by Khan et al. [87]. AuNPs were biologically synthesized using the extracts of *Suedafruciotosa*. The results highlighted that the photocatalytic activity of bioreduced AuNPs depends upon the size, aggregation, irradiation time, and concentration of the catalyst.

5. Nanozymes for enzymatic degradation of pollutants

Laccase is an important oxidase class of enzymes produced by a wide range of microbes and plant sources. Laccases play an important role in the biodegradation of lignin, phenol, pesticides, and other polyaromatic compounds. Enzyme-immobilized nanomaterials have been reported as an alternative procedure for the enhanced bioremoval of hazardous materials from the environment [88]. Immobilization of enzymes into the polymer matrix provides stability and confers long time usage ability compared with the free forms [89]. Furthermore, the immobilization technique favors an ambient environment for the enzymes to cope with the harsh environmental conditions. A novel chitosan/mesoporous silica−based inorganic−organic nanocomposite was fabricated and immobilized into laccase enzyme for the degradation of 2,4-dichlorophenols, which were assessed by Qiu et al. [90]. The fabricated nanocomposite was found to be an excellent nanocarrier for the

laccase enzyme and exhibited a potent pollutant degradation rate and improved catalytic activity. Mahamoodhi et al. [91] developed laccase immobilized carbon nanotube/nanozeolite bionanocomposite for dye degradation. The results of the study confirmed the enhanced degradation of dye in the combination of laccase enzyme in a controlled manner. Furthermore, the enzyme properties remain unaltered at different environmental conditions. Comparative studies on the removal of pollutants from wastewater, concerning the free nanocomposite material and its immobilized enzymatic form, were reported in recent reports. Zhang et al. [92] compared the dye removal potential of carbon nanotube composite and its laccase-immobilized bionanocomposite form. The findings of the study explored the enhanced removal of dyes in the immobilized form (96%) than the free nanocomposite form (84%). High enzyme loading capacity and declination of agglomeration between the carbon nanotubes are the critical phenomena responsible for better activity.

6. Biogenic nanoparticles in the removal of hazardous contaminants

In the past two decades, the field of bionanotechnology has received considerable attention toward the synthesis of biogenic nanomaterials due to their low toxic nature and simple fabrication procedures. Biogenic nanoparticles were found to possess unique size, shape, stability, and biocompatibility compared with the conventionally synthesized nanoparticles. The utilization of biomolecules and biological systems such as microbes and plants for the synthesis of nanoparticles possesses several advantages over physical and chemical methods. However, each source has been proven to have a unique biochemical mechanism for the bioreduction of nanoparticles. To date, diverse groups of inorganic, as well as organic and quantum dots, are reported to be synthesized efficiently by biological methods [93]. Plants are recognized as suitable candidates for the biogenic synthesis of nanoparticles because of their diversity and abundant nature [94]. Phytochemical compounds present in the plant systems are believed to act as a capping agent for the reduction of metal ions, hinder metal nuclei coagulation, and result in the bioreduction of nanoparticles [95]. In the case of microbes, multiple biosynthetic pathways are responsible for the formation of nanoparticles. Microbial synthesis of biogenic nanoparticles can be broadly classified into two types, namely biologically induced mineralization (BIM) and biologically controlled mineralization (BCM). In BIM-charged molecules present on the surface of microbial cells, such as sugars, glycoproteins are involved in nanoparticles with bioreduction and precipitation [96]. In BCM, nanoparticle synthesis is exclusively proceeded in a controlled manner by specific gene clusters. The formation of magnetosomes by magnetotactic bacteria is a good example of the BCM process [97]. In addition to the aforementioned mechanisms, biogenic nanoparticle synthesis is also carried out by organic electron donor and acceptor molecules intracellularly under aerobic and

anaerobic conditions [98]. In both cases, enzymes and secondary metabolites are considered as the key players in the biogenic fabrication of nanoparticles. The application of biogenic nanoparticles in the removal of different environmental contaminants is listed in Table 2.3.

Table 2.3: Biogenic nanomaterials in the removal pollutants.

Adsorbents	Contaminants	pH	Time (min)	Dosage	Reference
Radionuclides					
Alg—AA—VSA/f-MWCNTs	^{60}Co(II)	5.0	180	2.0 g	[99]
α-Fe_2O_3 particles	U(VI)	5.44	48 hrs	1.0 g	[100]
AC-PBNP	Cs^+, Sr_2^+, and Co_2^+	6.8	180 min	0.05 g	[101]
Starch-AA-VSA/ f-MWCNTs	Eu(III) and Cs(I)	5.0, 8.0	300 min, 180 min	0.01 g	[102]
MWCNTs	Cs(I)	10.0	80 min	0.05 g	[103]
Cellulose/HO_7Sb_3 nanocomposite	La(III),^{60} Co(II), and Cs(I)	5.5, 6.0 and 6.5	120min	0.05 g	[104]
rGONF nanocoposite	U(VI), Th(IV)	3.5	180 min, 150 min	0.4 and 0.3 g	[105]
Fe_3O_4 bionanocomposite	Sr(II), Th(IV), and U(VI)	5.0 and 3.0	48 hrs	0.20 g	[106]
Bacillus subtilis/Fe_3O_4 nanocomposite	U(VI)	4.0	120 min	0.3 g	[107]
PAN/AgX/ZnO nanocomposite	U(VI)	7.5	60 min	0.1 g	[108]
Magnetic zeolite nanocomposite	Sr(II)	12.0	60 min	0.2 g	[109]
Pesticides					
Chitosan —ZnO Nanoparticles	Permethrin	7.0	90 min	0.5 g	[110]
MHMS-MCNPs	Diazinon, phosalone, and chlorpyrifos	2.5	3 min	2.5 g	[111]
LFCOs nanoparticles	Vitavax	7.0	40 min	3 g	[112]
Pd nanoparticle loaded TiO_2Photocatalysts	Paraoxon	-	120 min	0.02 g	[113]
Fe—TiO_2/Bent-Fe photocatalyst	Diazinon	5.6	30 min	0.5 g	[114]
Fe/Pd bimetallic nanoparticles	DDT	10.0	30 min	0.55 g	[115]
Copper chitosan nanocomposite	Malathion	2.0	16 h	1.0 g	[116]
Fe_3O_4/graphene nanocomposite	Triazine	5.0	70 min	0.5 g	[117]

Alg—AA—VSA, alginate—acrylic acid—vinylsulfonic acid; *LFCOs*, $LaFe_{0.9}Co_{0.1}O_3$ and $LaFe_{0.1}Co_{0.9}O_3$; *MHMS-MCNPs*, mixed hemimicelle SDS-coated magnetic chitosan nanoparticles; *MWCNTs*, Multi walled carbon nanotubes; *PAN/AgX/ZnO*, polyacrylo nitrile/Ag zeolite/zinc oxide nanocomposite; *rGONF*, reduced graphene oxide—based inverse spinel nickel ferrite.

Edison and Sethuraman [118] designed a robust protocol for the rapid synthesis of silver nanoparticles using *Punica granatum* peel. The spectroscopic studies confirm the phytochemicals gallic acid and ellagic acid derivatives present in the peel were responsible for the fast reduction of silver nanoparticles. The green-reduced silver nanoparticle was found to possess an excellent green catalyst for the reduction of organic pollutant 4-nitrophenol. The additive effect of $NaBH_4$ for the catalytic reduction of p-nitrophenol to p-aminophenol in the presence of *Trachyspermum ammi* (ajwain) seed extract reduced silver nanoparticle was investigated by Chauhan et al. [119].

Magnetite nanoparticles find their extensive application in treating environmental contaminants such as heavy metals, textile dye degradation as nanoadsorbents due to their outstanding nature of simplicity, recyclable nature, and low cost. Furthermore, the magnetite nanoparticles can be easily separated from the medium by applying the magnetic field [120]. Kajani and Bordbar [121] reported the potential of the magnetite nanoparticle synthesized using the extracts of *Taxus baccata* L., by coprecipitation method. Additionally, the nanoparticles were tested for the adsorption of azo dyes and phenolic compounds in an aqueous solution. The adsorption results were well fitted with pseudo−first-order kinetics. Microbe-mediated size-controlled synthesis of FeS nanoparticles was developed by Yu et al. [122]. The findings of the study provided an environmentally friendly green protocol for the removal of heavy metal Cr (IV). Fathimah et al. [123] fabricated biogenic silica-supported iron oxide nanoparticles as photocatalysts for rhodamine B degradation.

Efficient removal of pharmaceutical waste by bacterially reduced biogenic platinum and palladium nanoparticles was reported by Martins et al. [124]. The biosynthesized nanoparticles exhibited excellent removal of highly problematic endocrine disturbing compounds such as ciprofloxacin, ibuprofen, and sulfamethoxazole in wastewater. Similarly, Annamalai and Vasudevan [125] investigated the role of self-assembled biogenic silver nanoparticles in the biodegradation of endocrine-modifying pollutant named di-(2-ethylhexyl) phthalate. Ameri et al. [126] evaluated the UV light−assisted degradation of diclofenac in the presence of biogenic selenium nanoparticles. Furthermore, the study optimized the rate of degradation using statistical methods and justified the combined role of UV light and selenium nanoparticles in the effective degradation of pharmaceutical waste. Debnath and colleagues synthesized zirconia nanoparticles using *Pseudomonas aeruginosa* in an eco-friendly approach and studied the sustainability in treating the pharmaceutical compound tetracycline. From the batch experiment, the removal efficiency of the tetracycline was found to be higher in pH 6.0 with an outstanding adsorption capability of 526.32 mg/g with a contact time of 15min. The adsorption values were found to be well fitted with the Langmuir isotherm and followed the pseudo−first-order kinetics [127]. Goswami et al. [128] prepared a nanocomposite using Pd nanoparticle synthesized

by resveratrol a polyphenolic compound obtained from plant extracts. The nanocomposite was further tested for its efficiency in removing the crystal violet, and it was found to be 99% with very good hydrophilicity with the breaking stress of 7.85 mPa.

7. Nanobiochar in the removal of organic and inorganic pollutants

Biochar is defined as low-density, high-carbon content porous materials produced from organic matter under anoxic conditions [129]. Biochar can be produced from different natural sources such as solid wastes, animal liters, cotton straw, water hyacinths, wood biomass, and crop residues [130,131]. Different methods, including pyrolysis, gasification, flash carbonization, and hydrothermal carbonization, had reported as efficient techniques for the production of biochar [132]. Biochar due to its large surface area and high chemical reactivity has proven to be an ideal material for the removal of diverse pollutants by the adsorption process [133]. However, biochar in its raw form holds limited adsorption potential in aqueous conditions [134]. The adsorption efficiency of biochar is dependent on physicochemical properties such as porosity, surface area, type of functional groups, and cation exchange property [135]. To improve the physiochemical property, biochars are subjected to acids, alkali, and oxidative agents to enhance their performance [136]. Therefore, immense efforts have been put forward to overcome the adsorptive limitations of biochar. The low density and small particle size nature of biochar are the major limiting factors that hinder the adsorption behavior of the biochar. Therefore, the development of magnetic biochar for the enhancement of adsorptive efficiency was attempted by several research groups [137,138]. Introduction of magnetic property to the biochar confers selective removal of pollutants through the magnetic field. Mallampati et al. [139] developed a novel carbon-based magnetic nanocomposite for the removal of methylene blue. Maximum removal of methylene blue was achieved at alkaline pH conditions. The findings of the study indicated that lower pH conditions resulted in the protonation of acid functional groups and competition between methylene blue and adsorption sites.

Recently, significant importance toward the development of biochar-based nanocomposites has been reported in scientific journals [140]. The application of biochar-based nanocomposites has proven to be an efficient technology for the elimination of pollutants from wastewater [141]. Furthermore, biochar-based functional nanocomposites were found to exhibit improved catalytic activity, surface activity, porous nature, and highly reactive functional moieties compared with their native form. Biochar-based nanocomposites are classified into three categories namely metal oxide-based nanobiochar, magnetic biochar, and functional nanomaterial-coated biochar nanocomposites. Each type of bionanochar material holds unique fabrication protocols, properties, and applications. Recent studies had explored that a combination of metal nanoparticles and biochar may overcome the drawbacks of individual material properties [142].

Liu et al. [143] fabricated iron- and nickel-doped bimetallic bionanochar using *Eupatorium adenophorum* weed-based biomass. The resultant metal-based bionanochar exhibited efficient (75%) removal of 2,4,6-trichlorophenols. The results of the study highlighted a simple and ecologically mitigating strategy for the elimination of 2,4,6-trichlorophenols. Enhanced removal of Cr(IV) by ZnO nanoparticle—coated biochar, derived from wastewater-grown hyacinth, was investigated by Yu et al. [144]. The synthesized biochar was stable at natural pH conditions with 95% Cr (IV) removal efficiency. Zhang et al. [145] developed a novel carboxymethyl cellulose (CMC) stabilized zero-valent iron nanoparticle-based biochar for hexavalent Cr (IV) removal. The results of the study substantiated the stabilization of the biochar by CMC composite over a wide pH range.

Furthermore, improper usage of antibiotics in the medical sector and livestock industries had led to the accumulation of antibiotics in the environment through domestic wastewater [146]. The persistence of antibiotics results in the development of antimicrobial-resistant strains. Huang et al. [147] studied the graphene oxide—coated bamboo dust—based biochar nanocomposites for the removal of sulfamethazine. The sorption potential of the nanocomposite was found to influence by pH, ionic strength, and $\pi-\pi$ electron donor—acceptor interactions. A novel molybdenum disulfide (g-MoS_2) nanosheet—decorated biochar was synthesized by hydrothermal method for the removal of tetracycline (TC) antibiotic-polluted wastewater [148]. The fabricated biochar nanocomposite exhibited excellent adsorptive potential and recycling performance for the removal of TC from river water. Similarly, Ma et al. [149] attempted the synthesis of nanoscale Fe- and Cu-coupled activated municipal sludge waste-based biochar composite for the removal of TC. Furthermore, the study explored the possible waste management approach for the utilization of municipal waste for the removal of pharmaceutical contaminants. A novel nanoscale *Pisum sativum*—based biochar encapsulated with starch hydrogel was fabricated for the removal of naproxen drug and chromium (IV) ions from wastewater [150]. The fabricated nanosorbent was highly stable and exhibited excellent swelling properties. Furthermore, the nanosorbent was found to eliminate both the naproxen and chromium at normal room temperature. Gowsami et al. [151] developed a bacteria-immobilized nanobiochar-based bed bioreactor for the treatment of biomass gasification wastewater. The study investigated and highlighted the feasibility of a biochar-coated bacterial biodegradation system for the combined detoxification of industrial wastewater and biomass gasification.

8. Adsorption mechanism and influence of physicochemical factors

Adsorption is generally a surface phenomenon in which the adsorbate gets attracted to the surface of the adsorbent. The interaction between the adsorbate and adsorbent is

influenced by various factors such as concentration, temperature, size, pH, and surface morphology of the materials [152]. Based upon the types of molecular bonding between the adsorbate and adsorbent molecules, the adsorption process can be classified into two types namely physisorption and chemisorption. The chemisorption process is favored by covalent bonding and electrostatic interactions. However, the physisorption process is based on the week van Der Waals forces between the adsorbate and adsorbent. Fig. 2.3 depicts the adsorptive behavior of biogenic nanoparticles in the removal of heavy metals.

Among the possible treatment methods, adsorption process is considered to be the best choice when compared with the other conventional methods. Also, adsorption technology holds additional features such as simple operative nature, less expensive, efficient, and recyclable nature. Most of the conventional adsorbents such as alumina, silica, clay, sand, and organic resins fail to exhibit high adsorption behavior, lack of cost efficiency, and reusability in the removal of diverse environmental pollutants. Application of nonconventional adsorbents, such as chitosan, starch, cellulose, alginate, rice husk, and microbe-based adsorbents, gained considerable attention in both scientific and industrial research. Fig. 2.4 illustrates the schematic representation of nanofilters for the removal of pollutants. These nonconventional adsorbents are inexpensive and abundant in nature and possess unique features in the removal of diverse environmental contaminants. In recent decades, numerous research efforts have been focused on the development of novel and highly effective adsorbents for the removal of environmental contaminants. Biobased nanoadsorbent materials have proven to be inevitable nanomaterials for pollutant elimination. These bionanoadsorbents overcome all the hurdles posed by conventional adsorbent materials. Especially biopolymer-based adsorption materials are found to be environmentally acceptable than their metal-based counterparts.

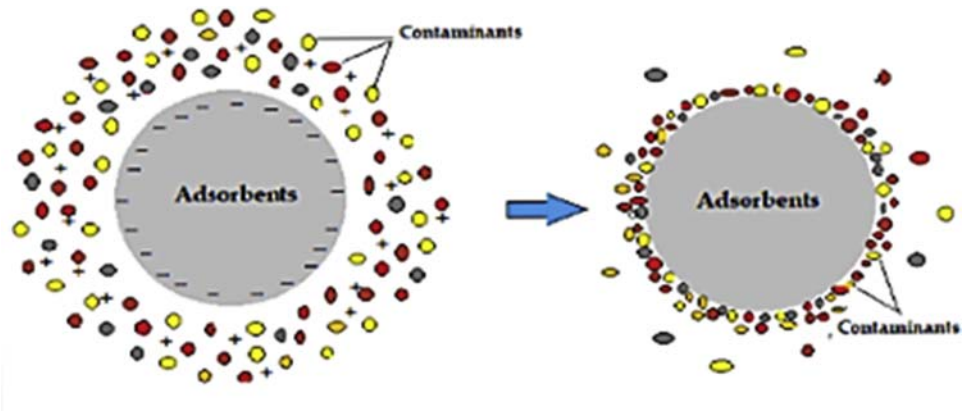

Figure 2.3
Adsorptive removal of heavy metals by biogenic nanoparticles.

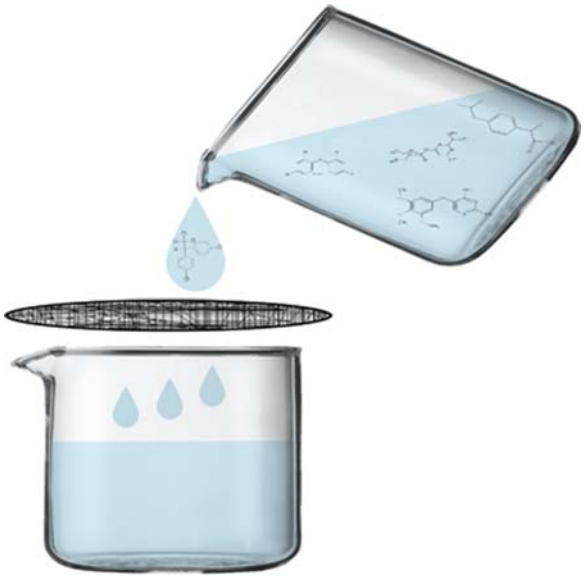

Figure 2.4
Schematic representation of nanofilters for the removal of environmental contaminants.

Apart from the development of novel functional nanomaterials for the adsorption process, validation of the adsorption process through statistical approaches is an important aspect in the elimination of contaminants [153]. To date, numerous adsorption isotherms and kinetic models such as Langmuir model, Freundlich model, Temkin model, Harkin Jura model, simple first-order, pseudo−first-order, pseudo−second-order, Elovich equation, and intraparticle diffusion kinetic models have been proposed and validated [154,155]. Table 2.4 represents the equation and constants of adsorption isotherm and kinetic models. The adsorption isotherm represents the amount of adsorbate adsorbed to the adsorbent at a given constant temperature. Among the proposed different adsorbent isotherm models, Langmuir model and Freundlich model are widely accepted and applicable for the diverse pollutant removal studies [153]. However, each of the models holds significant credentials in the prediction of the adsorption process. Langmuir isotherm predicts the uniform affinity of all the binding sites of the adsorbent to the adsorbate on a homogeneous surface. However, Freundlich adsorption isotherm describes all the uniform and uneven binding affinity of the binding sites of the adsorbent to the adsorbate in heterogeneous and multilayered surfaces. Temkin model is suitable for analyzing the interactions between strong electrostatic positively charged adsorbent types [156]. In addition to the adsorption isotherms, kinetic analysis of the chemical reaction between the adsorbate and adsorbent is essential to predict the rate of the pollutant removal process. Lagergren pseudo−first-order kinetic model is one of the old and highly studied kinetic models. However, Lagergren pseudo−first-order model is not a reliable model and is not applicable for the whole

Table 2.4: Adsorption isotherm and kinetics models [159].

	Adsorption model	Equation	Constants
Isotherm model	Langmuir Freundlich	$C_e/q_e = C_e/Q_{max} + {}^1/K_{ad}\, x\, Q_{max}$ $\log q_e = \log K_f + {}^1/(n \log C_e)$	C_e—equilibrium concentration of the contaminant (mg/L), q_e—adsorption equilibrium concentration (mg/g), Q_{max}—maximum adsorption amount (mg/g), K_{ad}—adsorption equilibrium concentration(mg/L), K_f—measure of adsorption capacity, n-adsorption intensity
Kinetic model	Pesudo−first order Pesudo−second order	$\log(q_e - q_t) = \log q_e - \frac{k_1}{2.303} t$ $\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e}$	q and q_e—amount of contaminant adsorbed (mg/g), t—time, k_1 (1/min)—pseudo−first-order rate constant of the equation calculated, from slope of the plot log $(q_e - q_t)$ versus t, k_2 (g/mg/min)—pseudo−second-order rate constant, t/qt versus t—yields a straight line with a slope of $1/q_e$, k_2—determined from slope of the plot

reaction time [157]. It is suitable for the assessment of 20−30 min of interactions. Therefore, the pseudo−second-order model is considered a good and reliable model for the assessment of the rate of the reaction [158].

Wang et al. [160] prepared a chitosan-decorated carbon nanotube (CS/CNT) implanted with magnetic nanoparticles (MNPs). The bionanocomposite was used as an adsorbent for the remediation of anionic azo dye acid red 18 (AR18). The kinetics of AR 18 adsorption showed maximum removal of 809.0 mg/g under 323.15 K. The adsorption process was evaluated with the pseudo−first-order kinetics and Freundlich and Redlich−Peterson isotherm models with an R^2 value of 0.9137. Kummer et al. [161] tested chitosan/nylon 6 and tannin/nylon 6 nanofibers as adsorbents for the removal of Cr (VI). The pseudo−first-order kinetics was best fitted for the chitosan/nylon 6 nanofibers-mediated Cr (VI) removal, while the tannin/nylon six nanofiber was fitted with Elovich model.

The pH is an important physicochemical factor considered to play a vital role in the adsorption process. A slight change in the pH alters the adsorbent surface properties and its degree of ionization. The impact of pH on the removal of methyl orange dye using

PVA/chitosan nanofiber/Fe(III) complex was ascertained by Ghourbanpour et al. [55]. The maximum dye removal efficiency was observed at acidic pH. In low pH conditions, the positively charged adsorbents get protonated and form electrostatic interactions between the negatively charged dye molecules and favor efficient dye removal capacity. Furthermore, the experimental data were best fitted with Freundlich adsorption isotherm and pseudo−second-order kinetic models. Alston leaf extract−reduced biogenic iron nanoparticle was synthesized by eco-friendly one-step reaction for the removal of Cr (IV) from wastewater [162]. The results of the study substantiated the role of electrostatic forces behind the removal of Cr (IV). Maximum removal of 983.2 mg of Cr (VI) was assessed by the pseudo−second-order kinetic model at low pH and high-temperature conditions. The metal removal mechanisms were achieved in three steps such as adsorption, reduction, and coprecipitation.

Al-Gorair [163] fabricated graphene oxide−entrapped arginine/chitosan magnetic bionanocomposite for the elimination of methylene blue from wastewater. The outcome of the results was best fitted with the pseudo−second-order kinetic model and Freundlich adsorption isotherm. Extreme adsorption behavior of the bionanocomposite was reported in alkaline pH 8. Furthermore, the thermodynamic study confirms the endothermic physisorption type of mechanism.

Pine wood−based nanobiochar was developed by Naghdi et al. [164] for the removal of pharmaceutical contaminant carbamazepine. The developed nanomaterial was able to remove 95% of the pollutant at a very low concentration (0.5−20 ppb). Optimization and adsorption models of the study confirm the nanobiochar material was able to retain its removal potential toward a wide pH range from acidic to alkaline conditions (pH 3 to 8). However, a twofold increase in the adsorption rate was witnessed at acidic conditions. Furthermore, the findings highlighted that the saturation of active sites in adsorbents at alkaline conditions may be the reason for the decline in adsorption rate.

Next to pH, the temperature is the second important factor that influences the adsorption process. Temperature determines the stability of the adsorbent and simultaneously controls the adsorption rate and behavior of the adsorbents. Furthermore, temperature influences the mobility and accessibility of the adsorbate in recognizing the active site of the adsorbent [165]. Temperature is also believed to be an important factor in determining the thermodynamic parameters such as Gibbs free energy (ΔG)-, enthalpy (ΔH)-, and entropy (ΔS)-associated adsorption process [166]. The batch adsorption assay was conducted by *Hibiscus sabdariffa*−mediated synthesized biogenic copper nanoparticles coupled with nanocarbon complex for the removal of nitrates [167]. Temperature-dependent change in the adsorption capacity of the adsorbent was observed. However, the fabricated biogenic adsorbent was able to adsorb nitrate even at a high temperature (45°C). A similar kind of response was reported by Al-Gorair [163] in the removal of dye methylene blue using

arginine/chitosan magnetic bionanocomposite. The adsorption rate was found to be high at endothermic conditions. Jagadeesan et al. [168] evaluated the effect of temperature for the removal of anthracene by photosynthesized magnesium/carbon nanocomposites. The experimental results confirmed the decrease in the adsorption potential of the nanocomposite with an increase in the temperature. The exothermic condition of the reaction may be due to the weak bonding between the pollutant and the active site of the adsorbent. The result of the study was according to the report of Dong et al. [169]. Crini et al. [170] substantiated that the development of thermally stable nanoadsorbents not only favors the rate of the reaction, but sometimes it may also lead to the technical drawback of an increase in the operating cost.

Apart from the pH and temperature, the concentration of adsorbent is a notable parameter that is directly proposed to the adsorption rate. Ghourbanpour et al. [55] investigated the role of adsorbent dosage in chitin-based bionanocomposite for the removal of dye methyl orange. It is evident from the study that increase in the concentration of adsorbent from 10% to 30% dosage resulted in the enhanced removal of methyl orange up to (94.2%). Kalantari et al. [171] explored the efficiency of Fe_3O_4/Talc nanocomposite for the removal of heavy metals Cu(II), Ni(II), and Pb(II). Furthermore, the effect of different parameters such as adsorbent dosage, pH, and the temperature was optimized using response surface methodology. The finding of the study confirms the increase in the adsorbent dosage improved the removal of heavy metals. Also, the experiment highlighted that adsorbent dosage is an independent phenomenon in the adsorption process. Therefore, it is evident from the aforementioned experiments that the availability of a large surface area and the active site is a unique feature associated with the concentration of the adsorbent. However, sometimes increase in the adsorbent dosage may hinder the removal of pollutants. Razzaz et al. [172] investigated the effect of adsorbent dosage on the removal of heavy metals Pb (II) and Cu(II) with biofabricated chitosan-coated TiO_2 nanofibers. The results of the study showed a decrease in the heavy metal removal efficiency with an increase in the adsorbent concentration. An agglomeration of polymer nanofibers resulted in the blockage of active sites and hindered the removal efficacy. A similar effect was reported by Kebede et al. [56] in the removal of pharmaceutical contaminates by *Moringa stenopetala* seed—based biopolymer.

9. Limitations of bionanomaterials in wastewater treatment

Application of bionanomaterials in the treatment of wastewater garners considerable attention due to their technological performance compared with their synthetic counterparts. However, bionanomaterials exhibit certain negative properties such as low stability, toxicity, and agglomeration. Hence, standard protocols in terms of dosage and reactivity with other environmental entities should be addressed in both the in vitro and in vivo studies for a long-time perspective. An increase in the agglomeration rate of the nanoparticles may result in the

blockage of adsorption efficiency [173–175]. Furthermore, the effect of the biological source used for the synthesis of nanoparticles determines the nature and properties of the bionanomaterials. Application of pathogenic species may confer subtle toxic properties [176]. Therefore, it is always important to take utmost care to ensure the safety of bionanomaterials and their interactions with the environment in field conditions. Furthermore, an in-depth analysis of the handling and discharge of bionanomaterials after the treatment process is essential for the large-scale environmental remediation process.

10. Conclusion and future perspective

Bionanomaterials due to their unique properties such as low toxicity, high stability, and abundant occurrence in natural sources have transformed into indispensable materials for the treatment of environmental pollutants. Several biogenic nanomaterials such as metal oxides, nanobiochar, biopolymer nanofibers, and composites have proven to be a potent agent in the degradation of different pollutants including heavy metals, dyes, and pharmaceutical contaminants. Moreover, effective online monitoring of the degradation efficiency of bionanomaterials, concerning environmental parameters, will address the drawbacks in the optimization of the adsorption process. Apart from the fabrication of technically sound bionanomaterials for pollution abetment, the development of mass production strategy of these green materials will bring the fruitful implementation of the technology from the lab to land approach. Successful large-scale synthesis of biogenic nanomaterials will surmount the hurdles in the commercialization of bionanomaterials. Furthermore, in-depth analyses on the interaction of bionanomaterials with other environmental matrices need to be considered. More emphasis on the toxicological investigation of the processed bionanomaterials will enhance the value of bionanomaterials in the future.

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SECTION 2

Environmental applications

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CHAPTER 3

Bionanomaterials-mediated seed priming for sustainable agricultural production

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Abbreviations

AgNP	Silver nanoparticles
CAT	Catalase
GA_3	Gibberellic acid
NMs	Nanomaterials
nm	Nanometer
NPs	Nanoparticles
PEG	Polyethylene glycol
POX	Peroxidase
ROS	Reactive oxygen species
SA	Salicylic acid
SOD	Superoxide dismutase

1. Introduction

Nanotechnology can revolutionize agriculture and plays a significant role in producing food and crops [1,2]. Over the past decades, several patents and innovations have been developed to collectively promote the efficiency and profitability of agricultural approaches, including nanopesticides, nanofertilizers, and nanosensors, which involve lower inputs and waste generations relative to the conventional techniques and applications [3,4]. Silver nanoparticles (AgNPs) seem to be the most prominent nanomaterials used in industrial, biomedical applications, antimicrobial agents, skincare products, construction materials, water purification, and pharmaceutical products. Considering that agricultural applications of nanoparticles (NPs) must be economical, eco-friendly, biocompatible, and nontoxic, the synthesis of bioengineered agricultural NPs must be consistent with those criteria [5–8]. The plant-based materials appear to be suitable substitutes for the synthesis of biocompatible because of the versatility of their biochemical nature, nontoxic

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phytochemistry, nonpathogenicity, lower cost, and versatile reaction parameters [9,10]. In commercial agriculture, rapid and consistent germination and the emergence of seedlings are essential determinants of a productive establishment [11,12]. Germination begins with water absorption through mature seeds (imbibition). It ends with the extended embryonic axis, typically the radical, through the seed envelope, with the root protrusion and the radical axis [11].

α-Amylase is among the key enzyme involved in starch degradation as the seed is germinating, and then the seedlings are formed. It is only an enzyme caused by hydrolysis in the native starch granules. It synthesizes and catalyzes α- (1 → 4)-oriented glucose polymers in cereal germination to generate fragments subsequently broken by the other amylolytic enzymes [13]. Therefore, the improvement of α-amylase in the seed germination process is of great importance in carbohydrate research to support commercial production [14]. Most of the seeds preserved under air-dry conditions will have deteriorated, and seeds maintained for a more extended period would gradually reduce their viability because of spontaneous cellular damage, resulting in the aging of natural seeds and thus the reduction in crop productivity [15,16].

For sustainable agriculture, efficient germination of the seed is essential. Thriving early plantation appears to require rapid and consistent root growth. Conventional seed germination involves three major distinct processes as shown in Fig. 3.1, consisting of (1) cycle I: seed hydrolysis cycle for passive dry tissue imbibition, first associated with water

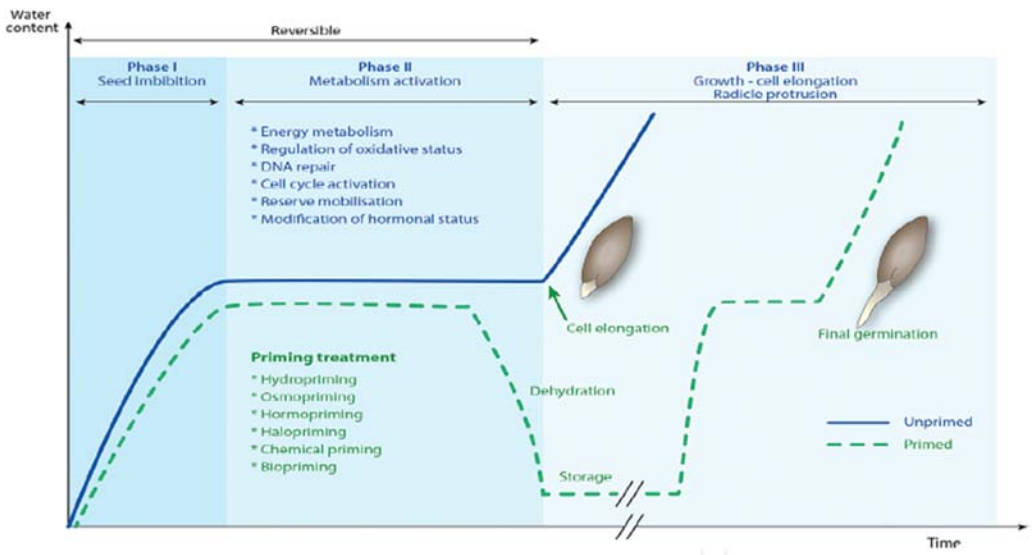

Figure 3.1
Seed hydration growth curves and germination phases during seed priming.

movement in apoplastic spaces; (2) cycle II: reestablishment of metabolic operation and mitochondria-level repair processes; and (3) cycle III: initially both cycles I and III suggest increased water content and hydration saturation during phase II. Germination remains a reversible cycle until just before the end of cycle II: seeds can be dried again and stay alive until processed. They can then be restarted on favorable conditions of germination. Water-based seeds are preseeding treatments that moisturize seeds partially without permitting them to grow [17]. During the reverse process of germination, different treatments can be used. The electrolyte potential of the priming solution, span, surrounding temperature, and presence of specific chemical components vary significantly. Successful treatments cause effective physiological activities throughout phase II of germination, which stops temporarily before drying loss (Fig. 3.1) [18]. The overall impact of seed priming is an enhanced seed capacity, defined as this unique combination of properties that condition seed lot efficiency in a wide range of environmental conditions [19]. Main methods can have many economic and agronomic benefits for cultivating plants. Extensive data available in the literature demonstrated significant improvement in germination rate and uniformity and a considerable improvement in the growth of plants and stress tolerance in young plants. While growers and seed companies have used priming for the past decade to strengthen germination, it can also exist in natural plant circumstances. More precisely, serotinous plants in desert areas will hold their seeds for a significant period. These seeds experience several hydrolysis−dehydration cycles, exacerbating germination after final dispersion due to excessive rainfall [20]. In general terms, the priming process concerns seeds and the whole plant system itself and can be characterized as an induced state in which a plant reacts to stress quickly and more efficiently [21]. Throughout this understanding, plants exposed to a significant restriction cause temporary metabolic adjustment, resulting in stress memory and helping them respond effectively to subsequent stress outbreaks [22,23].

Seeds priming is a technique that moisturizes seeds partly under a particular environment in natural or synthetic compounds but does not develop radical formation associated with germination. Seed priming has improved seed quality, seed production, crop yields, and increasing environmental stress tolerance [12,24]. Priming seeds may boost germination or even under adverse environments of tiny, damaged, or old seeds [15,24]. Numerous priming agents have been developed, which include polyethylene glycol (PEG), inorganic ions, and pure water. Nevertheless, different priming methods have other specifications, effectiveness, and standardization of priming agents for crop production. New priming agents for improving seed germination of diverse crop plants are therefore increasingly required [16,25,26]. Numerous metal-based NPs (e.g., AgNPs, TiO_2NPs, AuNPs, CuNPs, FeNPs, FeS_2NPs, ZnNPs) and carbon-based NPs (carbon and fullerene nanotubes) were used for seed germination, plant growth, and stress tolerance in certain agricultural plants in recent decades. Among these findings, quite a few scientists used a seed priming

approach that needs a seed to be redried until seeded to its initial moisture. Therefore, the process of nanoprimed seeds will differ from that of preseed treatment without draining seeds [27]. Thus, deep investigation on biochemical and molecular pathways of nanopriming effects for seed germination was not adequately explained. Many questions have been answered, especially the mechanism behind seed germination triggered by NPs [28–33]. While the interest in seed production has long been evident, this fascinating approach still has a weak understanding of the underlying physiological and biochemical basis. Holistic approaches to omics now give the molecular components of priming phenomena new possibilities for elucidation. Likewise, nondestructive and noninvasive methods such as digital imaging can be used to research the imbibition kinetics of seed ultrastructure in a more precise manner. This chapter discusses the latest developments made in understanding the nanobased seed priming approaches toward seed establishment.

2. A brief history of seed priming

Since the beginning of agriculture, seed physiology has been developed, and many seeds have not germinated uniformly and efficiently. Old culture was fascinated by the ability of a seemingly "dead" crop to regenerate and grow a healthy, viable young seedling after germination. The Greek Theophrastus (approx. 372–287 BCE) already reflected seed physiology and mentioned intermittent germination disturbance. Before sowing, Roman growers prehydrated their legume seeds to significantly boost germination rate as documented by Roman biologist Gaius Plinius Secundus or even harmonize seeds' germination. According to another French agronomist Olivier de Serres (1539–1619), similar practices were still used in a broad range of species. In 1664, Evelyn [34] reported that the prior sowing temperature could affect further germination, while Ingenhousz [35] studied the impact of light on the emergence of sowing after a century. During the 19th century, many botanists began to identify morphological processes linked to the germination of seeds [36,37]. In ancient times, the potential and profits of soaking seeds were identified and not neglected in the Middle Ages. The sap of onion cypress was first used as a soaking technique in Egypt, Greece, and the Roman Empire, and chlorine and manure were soaked in the Middle Ages [38]. However, its redevelopment from the 1960s has been modified and improved [18].

Furthermore, Sachs worked with various compounds (which include tyrosine and asparagine) during and before germination [39]. In the 1920s, plant hormone invention spotlighted the critical role of these hormones during germination in seed desiccation tolerance, reserve accumulation, cell proliferation, and cell expansion. The potential of preseeding to influence final germination led to a wide range of research procedures for several cultivated species of plants in the early 1980s [40].

3. Seed priming and its application in agriculture

Efficient and timely seeding is a critical prerequisite for crop production, especially under adverse environmental conditions. Techniques that positively impact vegetative growth and seed germination significantly affect yield and quality because of their robustness and tolerance to abiotic and biotic stressful situations [41]. The beneficial effects of priming treatments are dependent on various properties, as shown in Fig. 3.2. The best approach is to sort and throw away seeds that are too small and could be affected. Seed treatment has two primary groups, such as the soaking and dressing approach. The dressing is seed preparation with a chemical compound that does not penetrate the seed with an active substance. This process is designed to kill pathogenic substances on seed or soil surfaces. In addition, soaking is a seed treatment method that stimulates seed development and uniforms germination time. There seem to be three meaningful ways to soak: freshwater, soaking in a liquid or solid matrix, and immersion in a medium or low osmotic pressure [42]. The seed that either absorbs water or starts germination soaks up throughout priming. Germination can be divided into three phases. The first phase involves nuclear hydration,

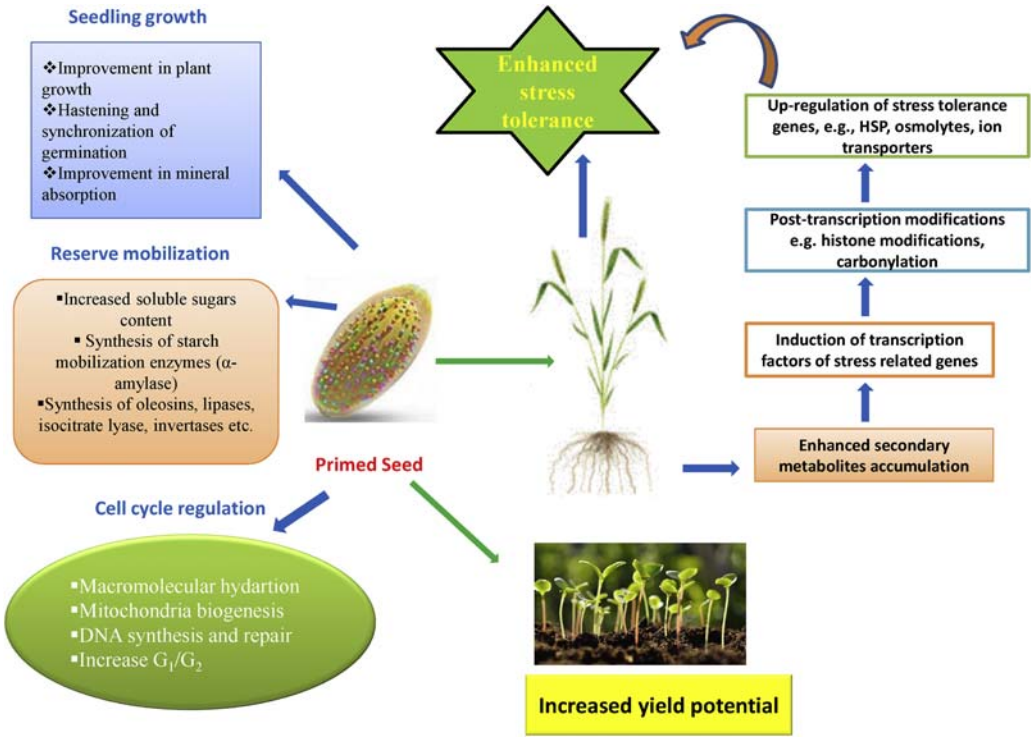
Seedling growth
❖Improvement in plant growth
❖Hastening and synchronization of germination
❖Improvement in mineral absorption
Reserve mobilization
▪Increased soluble sugars content
▪ Synthesis of starch mobilization enzymes (α-amylase)
▪Synthesis of oleosins, lipases, isocitrate lyase, invertases etc.
Primed Seed
Cell cycle regulation
▪Macromolecular hydartion
▪Mitochondria biogenesis
▪DNA synthesis and repair
▪Increase G_1/G_2
Enhanced stress tolerance
Up-regulation of stress tolerance genes, e.g., HSP, osmolytes, ion transporters
Post-transcription modifications e.g. histone modifications, carbonylation
Induction of transcription factors of stress related genes
Enhanced secondary metabolites accumulation
Increased yield potential

Figure 3.2
An overview of seed priming effects on seed ultrastructure by affecting the biochemical and physiological mechanism.

while the second phase triggers metabolic alterations and repair mechanisms [43]. Scientific understanding of these phases is meaningful since germination from the end of the second phase is irreversible; even before the end of the second phase, the seeds may be regenerated and saved until the seed can be sown to prevail, but without harm to the sprouts when sowing has been postponed. Different factors such as air circulation, temperature and relative humidity, durations, and seed quality directly impact priming effectiveness. In general, soaking cannot take longer than 6−12 h. If the seed cannot obtain oxygen for a long time, the cells are irreparably damaged, and then air supply is deemed necessary. The volume of water in seeds should be assessed to achieve an equivalent hydration level. The development of the drum method led to a more even absorption of water. The water consumption of seeds can be decelerated with wet organic or inorganic materials such as carbon or sand. In osmotic, however, the absorption of inorganic materials such as NaCl, KCl, or $MNSO_4$ in seeds should also be considered, while PEG may not be capable of entering the seed because of its size. However, it must be considered that some seeds also require a light or a sufficient germination temperature.

When the drying is finished, careful attention must be paid to drying, which should be slow and gentle. Furthermore, it must be recognized that all processes and measures of priming for the plant species should be optimized [44]. Although soaking seeds are the most well-known technique, its molecular and biochemical pathways are not adequately understood. The study also suggested that many species administering repair mechanisms support germination capacity. While priming does not directly impact cell division but progresses in the third germination stage, it enhances efficient and successful DNA synthesis before cell division, ultimately leading to the embryo's healthy development [42]. The synthesis of proteins essential to germinate occurs during the soaking process, taking more time without priming.

Furthermore, soaking helps to strengthen the antioxidant defense system [18]. While it offers many advantages, soaking seeds have not yet been widely spread and are generally used in horticulture and vegetable seed production. However, many research findings have been recently emerged to support more possible applications in addition to the three so-called soaking approaches. Currently, there are beneficial side effects of fungicides on planting, as some fungicides that have been initially applied to broad spectrums of seed have some possible biostimulant activities and may help resolve biotic and abiotic stress in the early stages of development [45]. Biopriming is a creative new method of defending seed from a pathogen when the seed is bacterial or fungus-coated [46,47]. By using biologically active, endogenous compounds might be used to increase plant productivity, as replacements of synthetic chemicals become even more essential. Plant stimulants (biostimulants), e.g., plant hormones including salicylic acid identified in willow bark and used as a priming material in traditional medicine and enhanced germination and seedling strength, are shown to act effectively as a priming compound [48,49]. Also present in all

living cells, polyamines, plant growth promoters were beneficial as seed soaking therapies to accelerate initial plant growth and defense against stress conditions [27,50,51]. The positive effect of ascorbic acid antioxidant has also been identified [52]. Also, the positive impact of ascorbic acid antioxidant was determined. There is no question that even better results can be obtained by applying such safe substances as certain foliar fertilizers. Nevertheless, while more and more foliar products are in the industry, such as an expanding range of plant extracts, only a few available descriptions are approved as seed priming agents [53,54].

A recent report has shown that seeds are consumed and preserved in a particular defensive substance (plant hormones and antioxidants) when used at appropriate levels but without adverse side effects [55,56]. Nonetheless, therapies such as moderate stress have plant negative effects, and—similar to training—genetic variation and synthesis of alternate defending molecules can contribute to a higher tolerance. These defending chemicals naturally accumulate in plants under extreme environmental conditions in response to plant stresses. However, significant improvements are not achieved in time and could adversely affect the growth of the plant. Our time is full of smart resources, and there is no justification for using an intelligent seed treatment technology. A recent study shows that the chilling resistance in maize seeds can be increased by using a plant hormone, a thermal sensitive hydrogel containing salicylic acid which improves the plant resistance to chilling. When the maize is subjected to low levels below 12°C, the hydrogel activates salicylic acid and its seed consequences resulting in enhanced germination levels.

In contrast, the youngest roots have a higher length and weight than uncontrolled roots [57]. In brief, natural antioxidants are highly promising to use as a seed priming product to connect biochemical activities during germination, unify growth, and improve crop resistance against several abiotic and biotic stresses. Such research findings demonstrate that the suggested range of application must be optimized and more realistic therapeutically combinations established. The positive effects on molecular and gene expression levels must be defined from a physiological perspective.

4. Application of different priming approaches and priming substances

Several methodologies have been introduced to strengthen seed and mitigate oxidative stress (Fig. 3.3). Restricted seed prehydration and quick germination are common elements of water-based priming approaches that separate them from all other presowing treatment options. Several factors affect priming efficiency and depend primarily on treated plants and selected priming methodologies. Physical and chemical characteristics, including solutes and water potential, priming element, period, temperature, light, ventilation, and seed state of health, also determine priming effectiveness and determine the percentages and the timeframe of germination, seedling vigor, and further seedling growth [58,59].

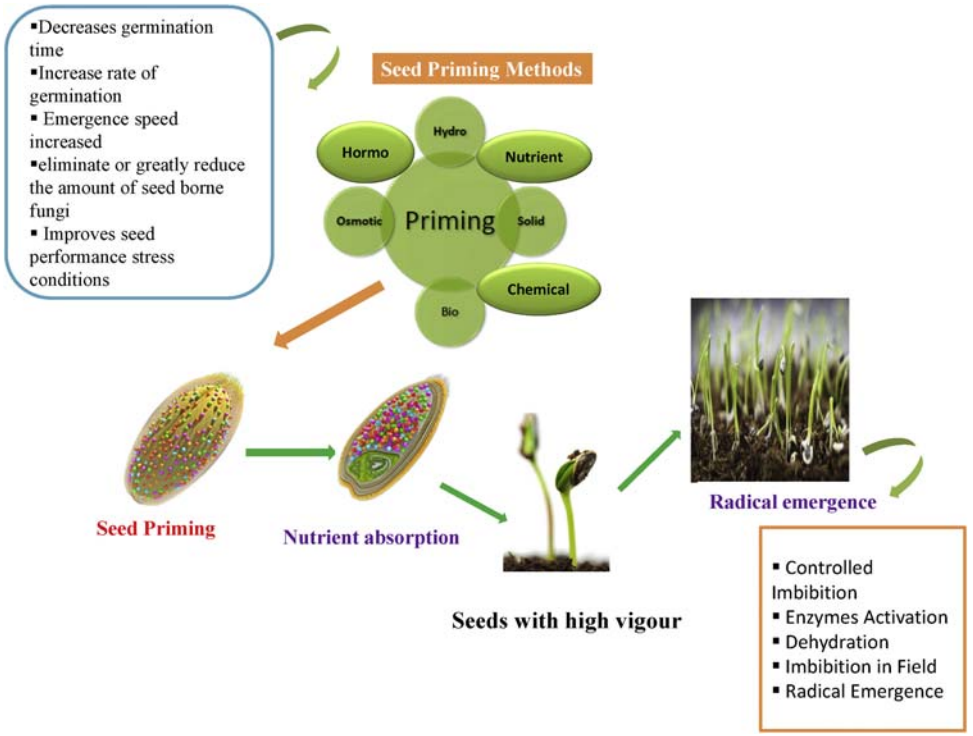

Figure 3.3
Different approaches of seed priming for seed establishment and their effect on seedling growth.

4.1 Nutripriming

Nutripriming is a procedure wherein seeds are soaked in solutions that contain the nutrient rather than pure water. The aim is to achieve a nutritional impact and the biochemical benefits of prime seeds to enhance seed efficiency, germination parameters, and seedling [60]. In low-root areas, zinc-based priming products increased chickpea and wheat productivity, rice germination and flowering, maize plant development, and root growth [61]. Although K-based priming product had a significant impact on increasing cotton seed germination in salt-affected soils and better nutrient uptake [62]. Crop companies also use specific nutrient techniques in the manufacture and preparation of seeds for crops. A broad spectrum of nutrient seeds is based on one of these methods. It has been shown to fertilize the seed and provide accelerated growth nutrients in a combination of elements such as zinc, copper, phosphorus, and molybdenum with significant germination outcomes, seed vigor, and the production of the root system.

4.2 Hydropriming

Hydropriming is the most basic seed priming process, based on soaked seeds in deionized water and redrying to the original moisture content before the sowing. This approach is of

low cost and environmentally sustainable without the use of additional chemical compounds as a primer. Uncontrolled water absorption by seeds is the critical drawback of hydropressure. This is because the seed is free to use water during hydropriming, so the consumption rate only depends on the seed tissue's water affinity [63]. This technique may also result in uniform hydration of the seeds, leading to a nonsynchronized emergence of simultaneous metabolic stimulation within the seed. In terms of these limiting factors, the exact duration of treatment, temperature, and volume of water used in hydropriming is critical to ensure a sufficient degree of seed hydration and prevent radical outbreaks. Despite these limitations, several reports suggested positive results in different crop crops such as maize, chickpeas, canola, durum wheat, wheat, capsicum, sunflower, rice, mung bean, and mustard on hydropriming and seedling growth in optimal as well as stress conditions. One of the hydro priming methods commonly used is the "drum priming" method, which was first documented in 1990 [64]. The seeds are rotated gradually in a drum and slowly hydrated in a vapor form by adding water in the drum priming process. Drum priming allows controlled imbibition of seeds and maybe an enticing alternative to traditional hydropriming. The specially constructed equipment allows seed weight control, time, and water quantity to be precisely controlled during the hydration cycle, resulting in a suitable and consistent seed moisture level [65]. Hydropriming with 24-epibrassinolide exhibited beneficial effects on the germination rate and with enhanced dismutase superoxide (SOD), peroxidase (POX), and catalase (CAT) in bell pepper seedlings. Another version of hydropriming, known as "on-farm priming," consists of seed soaking in water followed by drying and then seeding. Treatment duration must not exceed the "threshold level" (optimum priming period without risk of seed damage or premature germination). Harris et al. [2001] confirmed the beneficial effects of this approach on seed emergence and crop yield [66]. On-site priming is particularly useful in marginal tropical environments for resource-poor farmers.

4.3 Solid matrix priming

The solid matrix priming (SMP) was established as an alternative approach to osmopriming due to high osmotic potential and aeration problems. The water intake regulates the seed germination rate [18]. For a certain amount of time, seeds are mixed during firm matrices and incubated with the wet firm water carrier. Subsequently, the seeds are removed, washed, and dried from the matrix. Solid matrix use helps the seeds imbibe water gradually and activates the soil's natural soaking cycle [67]. To produce an effective SMP, products used as matrices must have unique physical and chemical characteristics, such as low solubility in water, low matrix strength, high water retention capability and surface, no seed toxicity, and binding ability to the surface of the seed. Peat moss, sand, vermiculite, soil, clay, and other substrates, such as microcell, are exemplary solid carriages used for definite matrices. Treatment times and optimum water content have to

be calculated individually for each matrix [68]. In several studies, the beneficial impact of SMP on seeds has been reported. The strong matrix priming increased carrot field performance and enhanced germination and soybean seed vigor. Onion research has shown that seed germination, seedling emergence, and growth under optimum and low-temperature conditions have improved seed conditioning. In addition to enhanced germination and plant growth in high-salt stress situations, sand priming may enhance the production of antioxidative enzymes such as CAT, POX, and total soluble sugars in waxy maize [69]. The combination of SMP with biological and chemical factors has improved seed performance [67] significantly. Likewise, gibberellic acid (GA_3) conditioning improved the consistency of hot pepper seeds [70]. Recent studies showed that the SMP with *Trichoderma viride* increased the seedling growth and yield at low temperatures in okra.

4.4 Osmopriming

In osmopriming, the seeds are soaked with low water capacities in osmotic solutions instead of pure water. Due to the low water capacity for osmotic solutions, the water gradually reaches seeds, permitting slow water imbibition, leading to early germination stages. Still, it averts the radical protrusion [42]. The water holding capacity of the osmopriming agents usually ranges between −1.5 and −2.5 MPa. Nevertheless, potential water values and the length of the priming treatment also need to be tailored to species, cultivar, and seed number. Specific compounds such as mannitol, sorbitol, PEG, glycerol, and inorganic salts include NaCl, KNO_3, KCl, KH_2PO_4, $CaCl_2$, K_3PO_4, and $MgSO_4$ are used in osmopriming processes [71]. The use of salt solutions is also known as halopriming. PEG is the most common chemical used in osmopriming, primarily because of its unique characteristic. The high molecular weight of PEG inhibits the penetration into the seed, thereby preventing undesirable cytotoxicity and osmotic ability of the seeds [42]. However, PEG has specific detrimental characteristics, such as high viscosity, which restricts the dissemination of oxygen into the solvent. It is preferred to use a PEG priming aeration system [18]. PEG seed priming has proven to be a successful way of improving the germination, sowing, and stress resistance of many crop plants in adverse conditions such as salt, soil, and chilling stresses [17,19,71].

4.5 Hormopriming

During hormopriming, the imbibition of seeds tends to occur in the vicinity of plant growth regulators that can affect seed metabolism directly. Hormopriming typically uses the following regulators: abscisic acid (ABA), auxins, gibberellin, kinetin, ethylene, polyamine, and salicylic acid (SA). Hormopriming via GA_3 and PEG potentially enhanced the plant growth characteristics viz. increased photosynthesis, seed emergence, antioxidant mechanism, and development of white clover polluted oils with heavy metal ions. GA_3 priming improved grain yield, salinity tolerance, hormone homeostasis modulation, ion

uptake changes, and aggregation between roots and shoots in spring wheat [72]. After kinetin priming, enhanced tolerance toward salinity, improved growth, and increased wheat grain yield were also observed [73]. The most successful method for inducing drought tolerance in rice was the pretreatment of spermidines among the various approaches of seed priming (halo-, osmo-, and hydropriming). Farooq et al. have also shown the high efficiency of polyamine priming for improving rice tolerance for drought [74]. In ascorbic acid and SA-pretreated wheat seeds, a critical function of phytohormones exogenously given in plant response to salinity stress has been noted. This pretreatment enhanced the capability of wheat seedlings to grow under high salinity successfully. At the same time, hormonal ABA priming was not effective in this case.

4.6 Chemical priming

Chemical priming means the treatment of seeds with diverse chemical solutions, which are being used as priming agents. This methodology encompasses a broad spectrum of natural and chemically synthesized substances such as thiourea, sodium nitroprusside, mannose, hydrogen peroxide, urea, fungicides, antioxidants (e.g., glutathione, proline, ascorbic acid, and melatonin), and selenium. Numerous studies have shown the beneficial effects of chemical-based priming by using different priming agents under diverse environmental conditions [75,76]. The β-aminobutyric acid seed priming improved drought and green gram's salt tolerance. As a priming agent, ascorbic acid has been used to cause drought and salt resistance to wheat [52,77]. Fercha et al. showed that chemical priming with the ascorbic acid reduced the harmful impacts of salinity through alterations in metabolism, protein source, and storage protein abundance [77].

4.7 Biopriming

Biopriming involves the sowing of seeds together with bacterial seed inoculation. As a novel priming process, this treatment improves the seed germination percentage and uniformity and protects the seeds from seed and soil-borne pathogens. The hydration of pathogen-infected seeds would lead to more robust microbial growth and ultimately to a deterioration of plant health. Antagonistic microorganisms are an ecological solution to this issue during the priming process [78]. Also, certain bacteria used as biocontrol agents can colonize the rhizosphere directly and help the plant after the germination stage. Biopriming is a much more reliable solution to treating diseases than other approaches, such as grinding and film coating. Biopriming is an integral component of agricultural practice with plant growth–promoting bacteria [79]. Furthermore, biopriming with *Pseudomonas fluorescence* isolates in pearl millet improved the growth and increased resistance to downy mildew disease. Biopriming with rhizobacteria improved the germination characteristics in saline conditions for radish seed [80].

5. Nanopriming: a novel way for seed germination and seedling growth

Technology transfer and implementation in the agricultural sector continue to be poor due to the lack of quality seeds and other socioeconomic factors. Bailly claimed that generation of the free radicals and reactive oxygen species (ROS) throughout storage could lead to membrane peroxidation, cell organelle damage, and micro- and macromolecular damage inside and on the cell surface that generates many cracks and lesions on the surface of the seeds [81]. These modifications are generally seen as the major contributing factors to seed degradation by a chain reaction of reactive species. Developing emerging technological advancements that may weaken the seed deterioration process to sustain seed sustainability for a prolonged period is of enormous assistance for both the seed industry and seed manufacturers. NPs may be one way to preserve the viability and strength during storage, avoiding both biotic and abiotic stress losses. NPs comprised of various elements and organic products were documented to boost the germination and quality traits in several crops by modifying the seed deteriorating biological mechanisms by breaking the ROS [82,83]. Nanotechnology is defined as the next big frontier in agricultural sciences and takes a prominent role in processing agricultural and food production via efficient soil nutrient management [84]. Since spherical or faceted metal particles are usually less than 100 nm in size. Such NPs have a high surface area ($30-50\ m^2/g$), increased mobility, a tremendous catalytic surface, strong chemical reactions, efficiently dispersing of water, and abundant adsorption. This means that the nanopriming can increase nutrient uptake efficiency and thus improve the yield and nutrient quality in the edible sections and reduce soil accumulation.

Seed nanopriming is a method in which seeds are pretreated before sowing or planting with NPs [85]. Nanopriming is a revolutionary way to improve seedling vigor and increase germination percentage and seedling growth, as displayed in Fig. 3.4. The development of pesticide resistance and environmental contamination, one of the significant challenges for the agricultural industry, resulted from large doses of conventional chemical pesticides [86]. Research organizations have been forced to look for effective alternatives to pesticides for plants (both cost and performance). The introduction of metal-based NPs in the agricultural fields should be compatible with the requirements since nanopesticides, nanofertilizers, and nanosensors provide more efficient and environmentally friendly alternatives to traditional farming practices [87,88]. The advent of biobased nanopesticides with a gradual release and capable of gradually degrading active ingredients gives hope that chemical pesticides can be substituted more efficiently [89,90]. Fungal-dependent AgNPs, in particular, may be the most feasible alternative given their excellent antimicrobial ability for most biomedical and industrial applications [4,91]. The use of fungal-based NPs is beneficial because of their ability to act as both reducers and stabilizers compared with other microbes for many reasons; for instance, enzymes

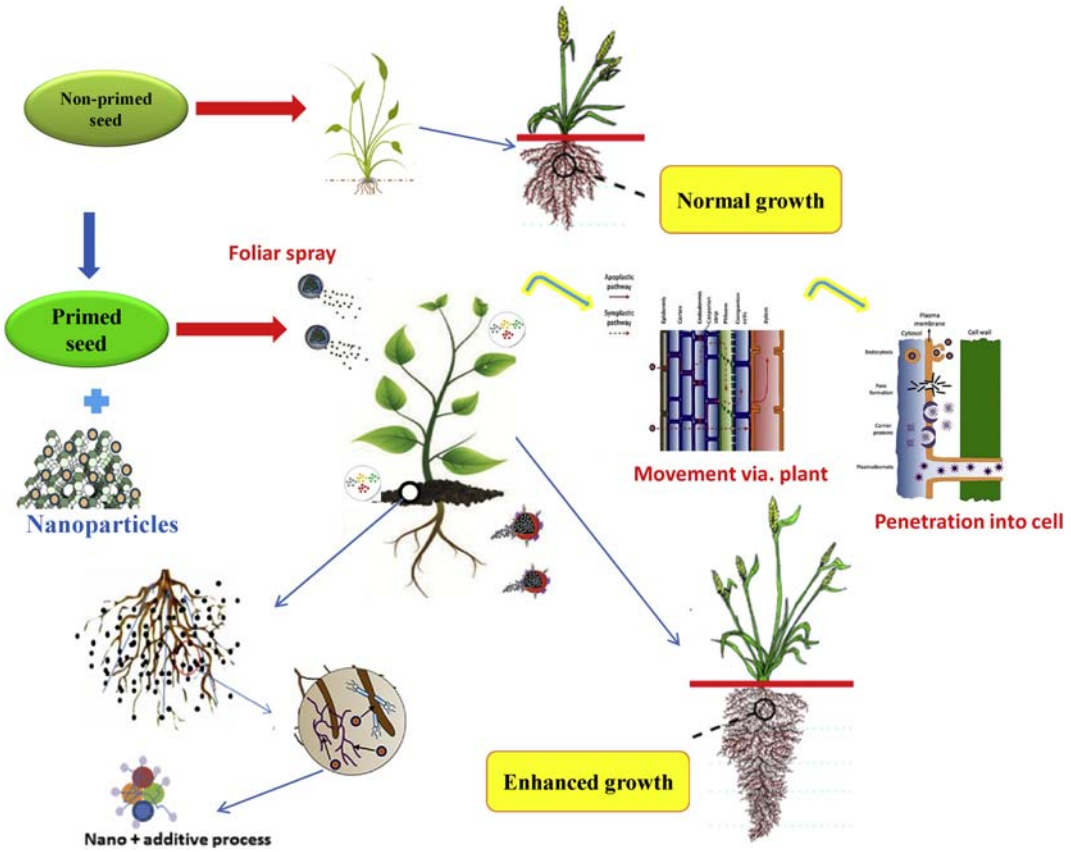

Figure 3.4
Interaction of nanopriming with seeds and plant growth. The NPs move through the plant cell. Apoplastic and symplastic ways enter the cells where they enhance the defense mechanism and promote growth regulators. In roots, they bind to root hairs, enter the cells, and improve the mineral and water uptake from the soil.

separated by fungi play an essential role in synthesizing silver NPs, but the detailed mechanism has still to be elucidated [92]. Several studies strongly recommended *Aspergillus fumigatus* in the rapid biosynthesis of AgNPs highly effective fungi against bacterial pathogens [93,94]. Although the mechanism behind it is not yet understood, there is a widely agreed mechanism. To conclude and generalize this, comprehensive work needs to be conducted. Fungi are favored among the microbial syntheses of AgNPs by (1) excellent extracellular enzymatic secretions, leading to the quicker production of AgNPs than chemical synthesis, (2) cost-effective and time-effective presence of the NP synthesis, (3) ease of efficient participation in fungal isolation, collection, processing, and storage, and (4) high return NPs [92].

The preparation of seeds with iron oxide NPs may be a safer way to tackle the question of the iron supply in alkaline soils. In this way, seed growth can be improved by specific biochemical and physiological changes [95]. Previous iron oxide NPs experiments have shown both stimulating and inhibitory effects on plants. While the positive impacts on *Capsicum annuum* plants were found, the bacterial soil method for wheat, watermelon, and ginger was used. Iron oxide NPs have also shown increased pest resistance to abiotic stress and physiological mechanism in plants [96]. The germination and growth in plants are influenced by NPs, and they also have antimicrobial activity in seeds. Seeds of oat and berseem treated with different concentrations of NPs viz. CuO, Ag, TiO_2, and ZnO had enhanced seed germinating characteristics [97]. Similarly, ZnO NPs treatment increased the germination rate and seed growth characteristics in groundnut [98], tomato [47], and maize [99]. Higher concentrations of Al_2O_3 NP increased the seedling's growth, soluble sugars, carotenoids, and protein content.

The nanoscale SiO_2 and TiO_2 mixture has been shown to increase the activity of nitrate-reductase in soybean (*Glycine Max*), enhance water absorption and usage, enhance its antioxidant function, and accelerate its germination and growth [100]. Besides, nano-TiO_2, photosynthesis, and nitrogen metabolism have been promoted, thus significantly enhancing spinach development at specific concentrations [101]. Some of its adverse effects on plant growth were the inhibition of seed germination and root biomass development, which varies considerably depending on the structure, composition, scale, concentration, and type of plant species. Root elongation of 5-day maize (*Zea mays*) was confirmed to have decreased at 2000 mg/L of alumina (nAl_2O_3) NPs while the cucumber (*Cucumis sativus*), mustard (*Brassica napus*), radish (*Raphanus sativus*), lettuce (*Lactuca sativa*), and ryegrass (*Lolium perenne*) had no effect under the same conditions. Lin and Xhing reported that suspensions of Zn and ZnO NPs at 200 mg/L concentration considerably impeded the root growth of the maize (*Z. mays*) and prevented the root growth production of other five plant species, while nAl_2O_3 (13 nm) prevented the root growth in maize, soya bean, mustard, and carrot at a concentration of 2 mg/mL [102]. NPs have very ambiguous effects on germination percentage. While NPs have been shown to improve the germination rate or have no impact on seed germination, several researchers documented the detrimental effects of NP in seed [103].

The limited literature on the effect of silver NPs on plant growth related to antimicrobial properties is available. AgNPs increased the seed germination at low doses (745 mg/kg seed), while at higher concentrations, they decreased the growth of seedlings toward germinating at the opposite [82]. For TiO_2, several researchers reported encouraging plant growth and the development of metabolites. Singh et al. and Rezaei et al. observed that the increasing concentration of TiO_2 enhanced the germination and growth of the plant due to altered enzyme activity [47,104]. NPs have a greater surface area due to their nanosize (10^{-9} nm), which increases the catalytic behavior and is extremely unstable.

It has also been demonstrated that NPs offer electrons that drench ROS' influence together with free radicals. Zheng et al. reported a similar phenomenon in spinach in which TiO_2 NPs may expedite the germination of old seeds and significantly improve their vigor by removing free radical intermediates, which accelerate the seed deterioration cycle and often increase free-radical enzyme concentration. It also makes the seed absorb more energy, allowing germination [32]. TiO_2 and SiO_2 NPs have been reported to improve the germination percentage and growth in soybean seedlings by increasing the amount of nitrate reductase enzyme and its capacity to uptake and mobilize water and nutrients, induce its antioxidant function, and, therefore, accelerate its growth and germination. The carbon nanotubes (CNTs) have been identified to enhance the seed germination rate and root elongation of tomato and rabbit radish seeds and rape seedlings [105]. NPs exhibited increased antioxidant activities and radical scavenging behavior during biochemical assay; consequently, the deteriorating cycle of ROS may have affected seed germination characteristics. Significant effects of TiO_2 nanosized on spinach germination were probably due to the small particle size that allows the NPs to enter the seed during the processing period with enhanced metabolic functions during the development [32]. The aging principle of the antimicrobial impact of NPs was identified in a blotter study, and AgNPs were shown to be robust antimicrobial agents [82].

Cellulose, chitin, and starch are plentiful, healthy, organic, and biodegradable (or whiskers) molecules. In most cases, the aqueous suspensions of these nanocrystallites are natural and, in laboratories, synthesized by acid hydrolysis. However, both good and weak chemical reducers and protective agents are used to make synthetic nanomaterials using physical and chemical methods. The development of bionanomaterials could open up novel applications in plant biotechnology and soil science. It is anticipated that the industrial production of manufactured NPs will soon be increased by manifold and released into the market. However, with significant potential benefits, considerable uncertainties regarding potential risks to the environment and human health need to be clarified.

6. Future perspective

The growth and production of plants are affected by all-metal oxide NPs. They generally encourage or delay germination, biomass accumulation, root/shoot elongation, and other biochemical and physiological processes [106]. Several crop species do not exhibit any morphophysiological improvement, while other plant species demonstrate significant alterations in the antioxidative enzyme activities and upregulation of heat shock proteins (*Hsp*). The plants have also developed a defense mechanism involving enzyme and nonenzyme components to prevent oxidative damage and enhance plant resistance to the toxicity of metal oxides. The precise and appropriate way of plant defense against

nanomaterial toxicity had not been thoroughly investigated. Thus, the mechanism of nanotoxicity remains uncertain; however, the chemical composition, particle size, surface, and structure of NPs should have been closely related [107]. Proper experimental design and analysis must be considered to provide appropriate knowledge and understanding of the biological effects of NPs. The first step in extensive and systematic research may be to explore the diffusion and transportation of NPs in plants to recognize the possible benefit of nanotechnology use in agricultural production [108].

With the present global supply versus demand pattern, nanopriming might be a future objective for sustainable agriculture [109]. A fortification program is a public health intervention that involves putting vitamins and minerals into packaged foods to improve the nutritional content of the food supply. The objective is to increase the population's healthy consumption [110]. As a consequence, biofortification reduces fertilizer and other agrochemical runoff into the environment, as well as their inputs. Stands have been formed due to seed biofortification, and plant production, yield, nutritional content, and water consumption have all risen, as has plant resistance to biotic and abiotic stressors [111]. The methodology has been discovered to become a simple, efficient, and cost-effective method of increasing seed and crop quality in resource-constrained areas. Seed priming using tailored nanomaterial generated more excellent germination rates at comparable or lower life cycle embodied energy than conventional seed priming. Due to its capacity to provide a wide range of designed nanomaterials in a much more effective way than before, nanotechnology also is a potent approach to supply nutrients effectively [112]. Minimal fertilizer might be used if seeds were nanobiofortified. As a result, fewer water and resources are required to produce the same amount of nutrient-dense food. Nanobiofortification of seeds may also help to reduce the growth cycle of plants (requiring less time for them to sprout and mature), allowing the land to yield harvests more quickly in the future. Seed nanoeffectiveness, biofortification's like that of other agronomic approaches, will be determined by how effectively it is tailored to the environment, which includes soil type, crop type, climate, and location [113]]. Other biofortification techniques, such as plant breeding and CRISPR/transgenic technologies, can give long-term and cost-effective solutions. In addition to analyzing the overall environmental consequences, it is critical to see if nanobased solutions are more feasible than traditional methods [114]. Nanomaterials are still being produced at greater scales, resulting in lower manufacturing costs. Nanotechnology will almost certainly be integrated with seed biofortification methods in the future, particularly if highly specialized and adjustable nanomaterials become available. Given the potential advantages and the rising global food insecurity that we will confront in the future decades, nanoenabled seed biofortification is an essential issue that deserves further investigation and attention.

In addition, several nanopriming studies used synthetic pretreatment methods for optimal growth under diverse environmental conditions. This observation implies the presence of molecular pathways for earlier priming events and memory imprints in nanoprimed seeds

[22,115,116]. Therefore, much additional research is needed to understand the systemic and memory footprints of seed priming and specific protein-related processes in plants, particularly the redox potential—based posttranscriptional modification period. Furthermore, it was proposed that priming requires the deposition of latent signaling components that are not being used before stress response issues [116]. Therefore, a comparative proteomic study should be carried out in plants treated with chemicals and before applying abiotic stress environments. Since nanopriming of seeds involves complex pathways, it is essential to classify different characteristics and potential interaction between them at the proteome level. Finally, a fascinating challenge would be the classic principle of priming in various biological systems and essential agronomic characteristics. For instance, Minas et al. conclusively proved that long-term ozone application during the cold storage of kiwifruit can act as an antiradical and antioxidant elicitor to make fruits tolerable to any subsequent ripening and senescence at room temperature [117]. Using proteomic approaches in plant priming agent, acclimatization is among the most recent advancements of fundamental and applicable research for a long time to come. In contrast, future proteomic priming studies may also help discover new seed quality markers, ensuring better crop production.

7. Conclusion

Seed priming with different priming agents (e.g., water, chemicals, etc.) maximizes the germination rate and seed quality characteristics in several crops. Nano priming is a new platform in the agricultural sectors, and its impact on various crops is still entirely unknown, as it has the potential to promote growth and to restricts its adverse effects according to its shape, size, concentration, intensity, chemical nature, length of treatment, and crop species. Numerous NPs could be used to address complex issues such as wide yielding varieties, early diagnosis of diseases, seed protection against various pathogenic fungi and bacteria, and plant growth management. Some NPs, including ZnO and Ag NPs, seemed to have antibacterial and antifungal characteristics that could be used to grow healthy or disease-free seedlings. Currently, food demand for the expanding global population is yet to be achieved; unsustainable chemical pesticides and fertilizers have been used, which pollutes the atmosphere and decreases agricultural productivity in that nanotechnology would, therefore, address these problems by the applications of nanopriming along with the use of nanofertilizers, which are required in lower concentrations than conventional fertilizer application. Even though the detrimental effects of NPs on the ecosystem, their incorporation into the food chain, and their impact on human health are still not fully explained, further research is highly required in this field before the extensive utilization of NPs in agricultural production. Interestingly, nanotechnology's existence remains to be determined owing to a few of the research community's controversial reactions to the application of NPs in the agriculture and food industries.

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CHAPTER 4

Reconnoitering bionanomaterials for mitigation of abiotic stress in plants

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Abbreviations

AgNPs	Silver nanoparticles
APX	Ascorbate peroxidase
CAT	Catalase
GNP	Gold nanoparticles
GPX	Guaiacol peroxidase
GR	Glutathione reductase
H_2O_2	Hydrogen peroxide
ION	Iron nanoparticles
MDA	Malondialdehyde
NMs	Nanomaterials
nm	nanometer
NO	Nitrous oxide
NPs	Nanoparticles
POX	Peroxidase
ROS	Reactive oxygen species
SOD	Superoxide dismutase
ZnO	Zinc oxide

1. Introduction

The world's population is expanding rapidly and may reach 9.2 billion by 2050. However, agricultural productivity is not through at the same pace. An exponential rise in population is a major challenge; as a consequence of increasing demand toward land for nonagricultural use, the area of production is likely to remain declining or even stagnant [1]. Although increased investments and technological breakthroughs will improve supply,

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this cannot automatically lead to greater accessibility and food absorption. Food security is of supreme importance for our changing climate. Climate change and increasing population are pushing scientists and agricultural engineers to innovate improved food production methods with less impact on the environment. As climate change progresses, abiotic stress is regarded as a significant constraint to drastically affect crop productivity [2]. Abiotic stress, one of the most critical risk factors for plant health and crop productivity, begins in the soil. According to one of the figures, 70% of the crop yield decline is affected either directly or indirectly by several abiotic stresses [3]. Abiotic stress results in a wide variety of biochemical, molecular, morphophysiological, and agronomical alterations that have detrimental effects on plant growth and production. Both natural and human-made activities affect the soil composition, leading to worsened growing conditions and deterioration the plant health. The most prevalent abiotic stresses include extreme temperature, salinity, drought, flooding, erosion, compaction, and contamination, which threaten global food security [4]. Drought, salinity, and nutrient deficiencies are some of these significant problems, primarily in developing countries, where rural people's incomes rely on agriculture [5].

According to a study by "The State of Foods & Agriculture 2007," only 3.5% of the world's land is not subsidence caused by environmental restrictions. The cultivation of stress-resistant plants can be a helpful strategy to address the problem of the decline in world food production. Farmers should modify agricultural practices and introduce positive nutrients and fungi to the soil for boosting them toward abiotic stresses. Conventional breeding methods have been very effective in improving crop tolerance achieved via intergeneric or interspecific hybridization programs. The complexities of stress resistance characteristics and limited genetic diversity of the grain yield and its components under abiotic stress conditions and the lack of an appropriate selection process limit conventional breeding approaches. Therefore, alternative strategies for growing stress-tolerant crops should be explored.

Nowadays, there is a demand throughout the world to enhance food production with finite resources, as well as using pesticides and fertilizers that can control environmental pollution and turn modern farming in the light of new agricultural technologies. A range of strategies is being pursued to improve abiotic stress tolerance, as well as the development of genetically modified organisms with specific genes functions that are expected to boost performance under stress conditions. In the era of agricultural and plant biotechnology, nanotechnology is one of the emerging technologies [6]. Nanoparticles (NPs) and nanodevices have a beneficial as well as a harmful impact on plant growth in different stages of development. Nanotechnology provides modern nanomaterial (NM) properties that are both easy to use for agriculture research for crop improvement and stress relief [7]. It is a versatile area and has been used in almost every field of science already known (Fig. 4.1) [8]. The use of NPs helps in improving the germination, seed

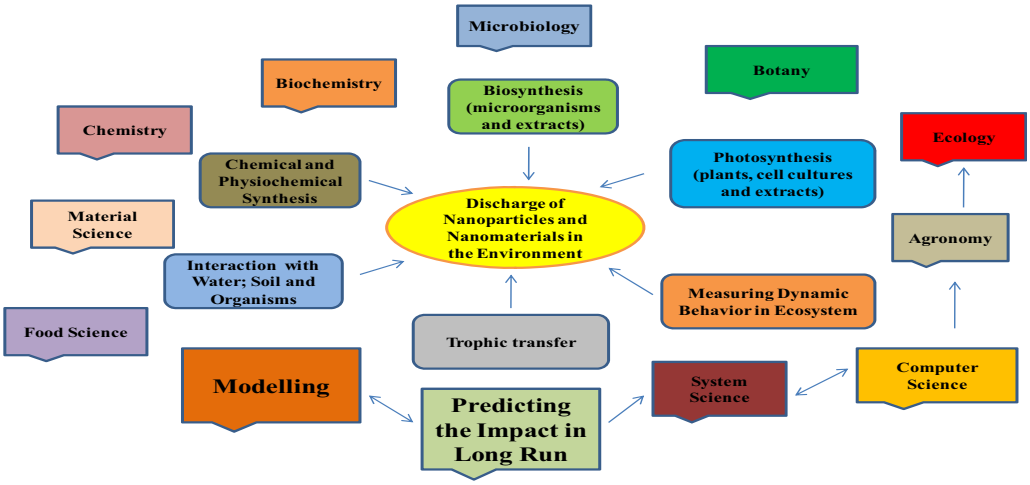

Figure 4.1
Scope of bionanomaterials in sustainable agriculture.

development, physiological activities such as photosynthesis and nitrogen metabolic, catalase (CAT), peroxidase (POX) and ascorbate peroxidase (APX) leaf activities, carbohydrates, chlorophyll content, protein, crop yield, and the positive modulations in gene expression, which indicate its ability to improve crop productivity. NPs increase resistance to drought by enhanced water uptake and root hydraulic conductance and display variations in protein quantity in oxidation–reduction reactions, detoxification of reactive oxygen species (ROS), stress signals, and hormonal tracts. NPs have very high mobility, which ensures that nutrients have easily been transferred to all areas of the plant. More specifically, by using nanopreparations, several approaches are being explored to enhance the resilience of crops under stressful environments. In provisional terms, nanotechnology is classified as structures, systems, and procedures operating around or below 100 nm (nm). Typically, "nano" corresponds to the spectrum between 1 and 100 nm. NMs consist of tiny components and affect the material properties at the macro level. The surface area of NMs is comparatively more significant compared with the same material mass that is produced in a larger form. NPs may increase the chemical reactivity of materials and affect their strength or electrochemical performance. NPs have a high volume/surface ratio to improve sensitivity and potential biochemical activity [9].

The effectiveness of bionanomaterials in combating stress depends on many factors, such as the timing of application and mode of action. The application of bionanomaterials may be performed at various times: before sowing, during, or after cultivation. These may be applied to seeds when plants are in early growth phases or when plants have been fully established according to desired outcomes [10]. Bionanomaterials containing antistress compounds, such as proline or glutamic acid, can be used during stress to alleviating their

harmful effects. On the other hand, those involved in the biosynthesis of bioactive compound activation must be implemented in advance of stress. Application timing during crop production is acceptable between species and depends on the grain filling stage, a critical phase for crop productivity. Identifying the appropriate period for applying bionanomaterials is as essential as the exact dose determination, so that waste is avoided; high production costs and unexpected outcomes are also avoided. Bionanomaterials may be applied as foliar or root sprays, to protect the seedlings in the early stages of growth, as a nutrient solution of the floating system, or during flower or fruit production. Bionanomaterials have become more and more concerned with the safety of plants. Such products can combat the environmental strains of water scarcity, soil salinization, and exposure to suboptimal temperatures of growth in various ways [11–14]. They improve plant efficiency, increase plant growth and productivity, influence plant response procedures, and increase antioxidant accumulation.

2. Bionanomaterials: a new frontier in plant growth and development

Nanotechnology is such a revolutionary technology that longstanding issues in agricultural production systems can be solved [15–17]. It was anticipated that nanotechnology would become a significant and essential part of the global food production chain, for instance, in crop defense [18,19], fertilizers [20], biosensors and precision farms [21], food packaging, and health [22]. NPs are all-encompassing in nature, and different types of NPs have evolved from plants [23].

As the sessile organism, plants can only cope with various environmental stresses during the life cycle; thus, by changing genetic, metabolic, and physiological routes, they improve their protection from different abiotic stresses at numerous levels. Plants use the molecular pathways by modifying gene expressions to combat under stressed conditions [24]. Several research findings and studies have shown that the NP-mediated impact on the plant developmental processes depends on its concentration. The activities of antioxidant enzymes such as superoxide dismutase (SOD), CAT, and POX are upregulated by NPs [25]. Laware et al. conducted a study to determine the effect of TiO_2 NPs exposures on seedling growth and observed that, with an increasing NPs concentration, its development also increases [26]. Seed germination and the growth of seedlings were increased in onion at low TiO_2 NPs concentration, whereas the effect was reversed (suppressed) at higher rates. There has been significant induction of hydrolytic enzymes (amylase) and antioxidant enzymes (CAT and POX, SOD) in a concentration-dependent manner. However, the activity of enzymes at lower levels (10–30 microns/mL) of TiO_2 has been higher (40 and 50 μg/mL). Several studies have suggested that TiO_2 and SiO_2 NPs have demonstrated the ability to improve the germination and growth of seeds in *Glycine max* [27].

In the area of nanotechnology, NMs exhibit various physicochemical properties as opposed to synthetic chemicals (such as a photocatalyst, silver nano, nanocarbons, carbon nanotube, silica, and fullerene). NMs such as single-walled C nanopore, dendrimer, quantum level, metal (silver, silicon, and gold), and metal oxides (TiO_2, SiO_2, ZnO, and CuO) are all common types of NMs that are being used in different applications. NMs could occur in natural and human-made processes (e.g., volcanic or diesel); these activities may accidentally lead to NM generation. There are two methods for producing NMs, one is the "bottom-up" method (for example, self-assembly), making nanoscale NMs from atoms and molecules, while the other is the "top-down" method (for example, milling). The NMs can be of a single size (such as films), two-dimensional (such as fibers), or three-dimensional (such as particles) [8,28–30]. These may exist in circular, tubular, and irregular forms as single, melt, aggregated, or aggregated shapes.

Carbon-based and metal-based NMs are a very new area of research recently used in plant science. Fullerene C_{70} ($C_{60}(OH)_{30}$) and carbon nanotubes are among the frequently studied carbon-based NPs, while metal-based NMs are Ag, TiO_2, Cu, CeO_2, Au, ZnO, and FeO NPs. Among the naturally occurring NPs, iron oxide nanoparticles (IONs) constitute an essential component from soil microbes and plants as reported in several reports [31–33]. Some researchers are concerned with the toxicity of engineered ION plants [34], while others focused on IONs as potential biofertilizers [35–37]. They also enhanced the growth and development of plants at a particular concentration in the chelated form [37]. As compared with conventional iron fertilizers, nanoiron oxide can stimulate plant growth via. its enzymatic capabilities. It has been suggested that magnetic NPs Fe_3O_4 and maghemite-Fe_2O_3 are efficient nanozymes of mimetic peroxidase (low pH) and mimetic catalase (neutral pH) ability [38,39]. During abiotic stresses such as salinity, drought, and heat, it aids plants by increasing the accumulation of antioxidative enzymes such as peroxidase and catalase to scavenge the ROS being released as toxic compounds. In plants, IONs act as nanozymes and reduce the harmful effects of hydrogen peroxide contents in *Brassica napus* leaves, and relieving oxidative stress [40].

3. Mechanism of action of different bionanoparticles in plants

Plants intelligently perceive, handle, sustain, or avoid environmental changing conditions [29]. They possess interactive metabolic intermodulations within diverse signal transduction networks and tracks to perceive ecological stimuli and respond to different abiotic stresses. In detecting abiotic stimuli and reacting to them in soil [35], the root architecture is the most sensitive. It is a complicated phenomenon involving complex and real-time changes at the stage of genesis, transcriptomics, cellular and metabolic, and physiological methods. Drought, cold, salinity, and heat have a significant and immediate effect on cells through water-deficient conditions followed by biochemical, molecular, and

phenotypic stress responses [41–43]. Plant stress may vary with the environment in which they sustained compared with individual stresses; the strength of their response may vary in multiple stresses. The difficulty is to activate particular gene expressions in response to individual stresses, accompanied by metabolic programming in cells [30,44–47].

The intake, absorption, and translocation of NPs are based on the plant species, size, form, chemical structure, functionality, and stability of NPs. NPs generally connect to the network via. lateral roots and enter the xylem via. cortex and pericycle [48]. The interaction network of NPs and the plant's system mainly focuses on the oxidative processes that generate ROS, activity in the transportation of ion-cell membranes, oxidative damage, and ion transporters. The NPs exhibit catalytic activity with sulfhydryl and carboxylic groups once they reach plant cells and eventually modify the protein function. The NPs can form complexes and be transported into plants by membrane transporters or radical exudates [49,50]. The NMs move from leaf blades to roots, stem, and grain and from one root to another root. One of the most common transit routes of uptake and transportations to the shoots and leaves is the xylem [51,52]. The NMs will penetrate the cuticle and reach inside the cytoplasm of cells [53] and interfere with the metabolism at that place [54]. The NMs could bind to various cytosolic organelles within the cytosol and impede the metabolic process [54]. One pathway that can also transport the NPs (20 nm) inside the cells is via. plasmodesmata [55,56]. Research on C_{70}-NM transmission in the generation of rice plants reported the occurrence of Black C_{70} aggregates in the second generation of plants when plants treated when with fullerenes only in their first generation [57].

Such particular interactions can mainly arise from its small scale, bulky surface area, and inherent biocatalytic activity, with biological systems, including plants, chemical, or mechanical interaction. A few studies only define NPs affecting antioxidative enzymes at the biochemical level and genetic change at the molecular level. They were treating silver nanoparticles (AgNPs) in *Brassica juncea* [58] improved antioxidant enzyme activities, which resulted in lower ROS concentrations and enhanced antioxidative enzyme activities, such as APX, guaiacol peroxidase (GPX), and CAT. The application of AgNPs of 6 nm was added at 5 mg/L, and the antioxidant system of *Spirodela polyrhiza* was activated, as shown by the SOD, CAT, and POX [59]. However, there was also an increase in ROS concentration, malondialdehyde (MDA), and glutathione content. In *B. juncea* sperm, the use of gold nanoparticles (GNPs) considerably enhanced the activity of antioxidative enzymes such as APX, GPX, CAT, and glutathione reductase (GR), accompanied by higher accumulations of hydrogen peroxide (H_2O_2) and proline [60]. Furthermore, the H_2O_2 and proline content are shown to increase, with an increment in the concentration of GNP. In particular, the activities are increased up to a GNP concentration of 400 ppm, with a maximum glutathione reductase activity, while at 200 ppm, GNP, APX, GPX, and GR were enhanced considerably. The exposure of NPs to CeO_2 in the kidney bean

produced antioxidant defense (APX, CAT, and GPX) responses in the leaves, stems, and roots [61]. On the contrary, AgNPs were mainly involved in signaling, Ca^{2+} ion regulations, transcription, cell wall biosynthesis, oxidative stress—responsive pathways, degradation of proteins, apoptosis, and cell division in rice proteomics. The effect of zinc oxide (ZnO) in the roots resulted in 550 up- and 820 downregulated genes' expression. The application of TiO_2 NPs in *Arabidopsis thaliana* resulted in 220 up- and 190 downregulated genes (expression difference of >2.5 folds) [62]. The induction of genes' expression by ZnO and fullerenes mainly involves ontological classes, both abiotic (oxidants, salt, lack of water) and biotic (wounding and pathogenic defense) stimuli, which have been noted as stress sensitive. Through many stress-related gene expressions, the application of multiwall carbon nanotubes had a significant effect on tomato seed germination and seedling growth [63].

Plants are an essential living part of the terrestrial ecosystem. The major contributing factors that reduce crop growth and productivity are alkalinity, salinity, drought, immersion, and mineral deficiencies among the different abiotic stresses [64]. The plants encounter a series of environmental challenges throughout their life pan; hence strengthen their survival by regulating the anatomical and molecular pathways; and establish protection at various levels. Plants adopt molecular pathways by modifying genetic expressions accordingly to overcome these constraints. Several studies have shown that the mediating effects of NPs on plant growth and development depend on the concentration. NPs can upregulate antioxidant enzyme activities, including SOD, CAT, and POX [26]. Tolerance, resistance, and vulnerability to stress are multiple phases of plant growth, including numerous events (Fig. 4.2). Instead of having an additional effect on plant health, the abiotic stress reactions could minimize or increase the plant's vulnerability to biotic stress-induced by pests or pathogenic substances [65]. In many farming systems, this is important because most crops grow under suboptimal environmental conditions, which restrict their genetic potential for growth and development [66]. The key components of stress tolerance are defense, repair, acclimation, and adaptation. Environmental improvements such as rewatering and cycled water conditions frequently occur [67]. Subject to severe water deficiency conditions can lead to a negative effect on the metabolism of antioxidants [68,69].

Rewatering further eliminates membrane peroxidation and stimulates the development and production of novel plant components and the opening of the stomata. Under drought conditions, their rehydration may contribute to a higher accumulation of H_2O_2 at the root level [68]. Drought responses differ from one plant to another with the function of the enzyme SOD, which is essential to the antioxidant metabolism [70]. The SOD behavior in bluegrass remains unchanged due to dry conditions and Fe-SOD, and Cu/Zn-SOD's gene expression decreases [30,71,72]. Fe-SOD and Cu/Zn-SOD can moderately tolerate droughts regulated in alfalfa nodules, which means responses may vary from species and

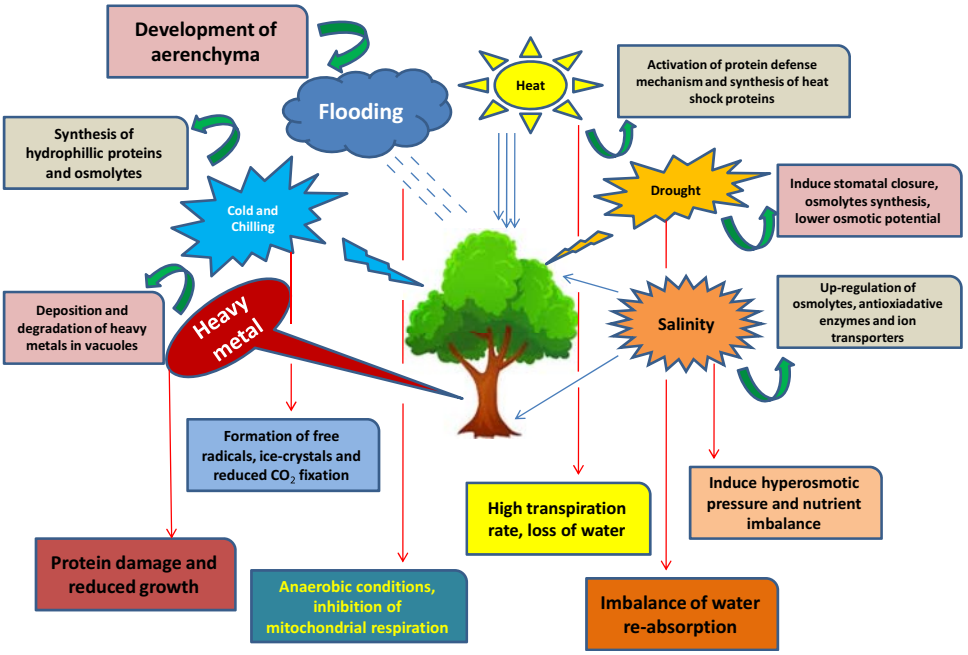
Development of aerenchyma
Flooding
Heat
Activation of protein defense mechanism and synthesis of heat shock proteins
Synthesis of hydrophillic proteins and osmolytes
Cold and Chilling
Drought
Induce stomatal closure, osmolytes synthesis, lower osmotic potential
Deposition and degradation of heavy metals in vacuoles
Heavy metal
Salinity
Up-regulation of osmolytes, antioxiadative enzymes and ion transporters
Formation of free radicals, ice-crystals and reduced CO_2 fixation
High transpiration rate, loss of water
Induce hyperosmotic pressure and nutrient imbalance
Protein damage and reduced growth
Anaerobic conditions, inhibition of mitochondrial respiration
Imbalance of water re-absorption

Figure 4.2

Different kinds of abiotic stresses and plant adaptive strategies. Under the adverse effects of temperature, salinity, chilling, and drought, the biochemical reactions are more or less identical. Higher accumulation of heavy metal ions and rise in temperature also have an equal effect. In plants where the aerenchyma is evolved to deal with anaerobic conditions, submergence/flood conditions lead to degenerative responses.

tissue [73]. An elevated level of soil salts is harmful to plant cells, and distinct tissue cells respond differently to salinity stress [74]. Stressed cells, whether at the root or in internal tissue, affect their neighbor cells and induce a shift in gene expression patterns [75]. The osmotic ability of the soil significantly decreases because of the high salt levels, which are essential as a result of ion toxicity combined with drought stress in plants. It can affect the plant's viability by preventing seed germination and seedling production, hindering plant senescence, and ultimately causing death [76]. It was identified that there were three significant salts overresponsive (SOS) genes, namely, SOS_1, SOS_2, and SOS_3 proteins, in the SOS stress signaling pathways [77]. Conditions of salinity decrease the amino acid levels, such as methionine cysteine and arginine. The proline synthesis in cells is a common salinity relief approach [78]. Similarly, nitric oxide production (NO), antioxidant enzymes and compounds activation, hormone regulation, glycine betaine accumulation, and polyols are some additional modifications of the plants [79]. This is predominantly due to lack of water and unavailability of nutrients associated with high salt levels, which cause severe considerable harm to plant tissue and directly impact productivity.

As the earth's temperature increases, thermal stress has become a major agricultural issue severely affecting cultivation. The temperature increase has a detrimental effect on plant morphoanatomy, physiology, biochemistry, or genetic alteration. Detailed knowledge of plant physiological changes in temperature and tolerance processes can contribute to the strategic implementation of innovative alternatives to crop production management [80]. Heat affects plants at different stages of growth, with high temperatures causing decreased germination of seeds, loss of photosynthesis and transpiration, and decreased membrane permeability [69]. Changes in phytohormone levels, primary and secondary metabolites, increased heat shock expression, associated proteins, and ROS production are a variety of prominent heat stress responses in plants. Mitigation techniques in plants include triggering mechanisms to help the preservation of membrane stability and induction of MAPK and CDPK cascades during high-temperature stress [81].

Furthermore, ROS scavenging, compatible solutes, antioxidant metabolite accumulation, and chaperone signaling and transcription modeling are some equivalent acts that enable the cells to manage thermal stress [80]. Rather than personal stresses alone, the multiple stress factors have more positive impacts on plant life. In short, the combination of stress decreases each other's adverse impact, improving the chances of better plant survival. The combined effect of drying and ozone accumulation (O_3) on plants has shown improved tolerance. According to Iyer et al. (2013), the cumulative impact was reduced stomach conductivity values [82]. Elevated glutathione and ascorbic acid reduction in concentrations are successful for free radical scavenging, contributing to a significant drop in overall ROS content.

Conversely, it is indeed difficult to understand the plant behavior patterns toward a single stimulus, especially when the combined impact of environmental stresses increases in the field. Multiple stresses arise in-field practices simultaneously; thus, multifaceted plant structures are present to cope with adverse circumstances that fluctuate rapidly. Though efforts have been made to assess the response of plants to single stress [65,83–86]. This restricts, in particular, our knowledge of plant reactions to multiple stress environments and the estimation of cumulative stress tolerance mechanisms in laboratory conditions or field conditions.

4. Bionanomaterials: use under different stress conditions

Rapid growth and wide-ranging nanotechnology applications have progressively increased the number of bionanomaterials of our live systems, which helps the plants cope with multiple abiotic stresses such as drought and salinity.

4.1 Bionanoparticles under drought

Water is essential for the survival of plants and necessary for the transport of nutrients. Thus, water shortage results in drought stress, leading to reduced plant vitality [87]. In general, drought has been considered a dangerous crop situation. Without sufficient soil moisture, plants could not grow to their full capabilities. In dry conditions, plants have shorter foliage and lighter shoot and seed mass, both in tropical and semiarid regions. Drought is a worldwide issue, and 12 million hectares of soil that can yield 20 million tons of grain are dropped every year due to drought stress. A growing market to counter the adverse effects of drought is beginning to emerge. Drought stress is reported to have severe consequences for crops, including reduced leaf area, reduced growth, limited carboxylation, decreased water potential, hormonal imbalance, and oxidative stress (Fig. 4.3). Nanotechnology promises a significant attempt to alleviate the impact of water scarcity (Fig. 4.3). NPs induced by different stresses are tested in many recent studies (Table 4.1) [88].

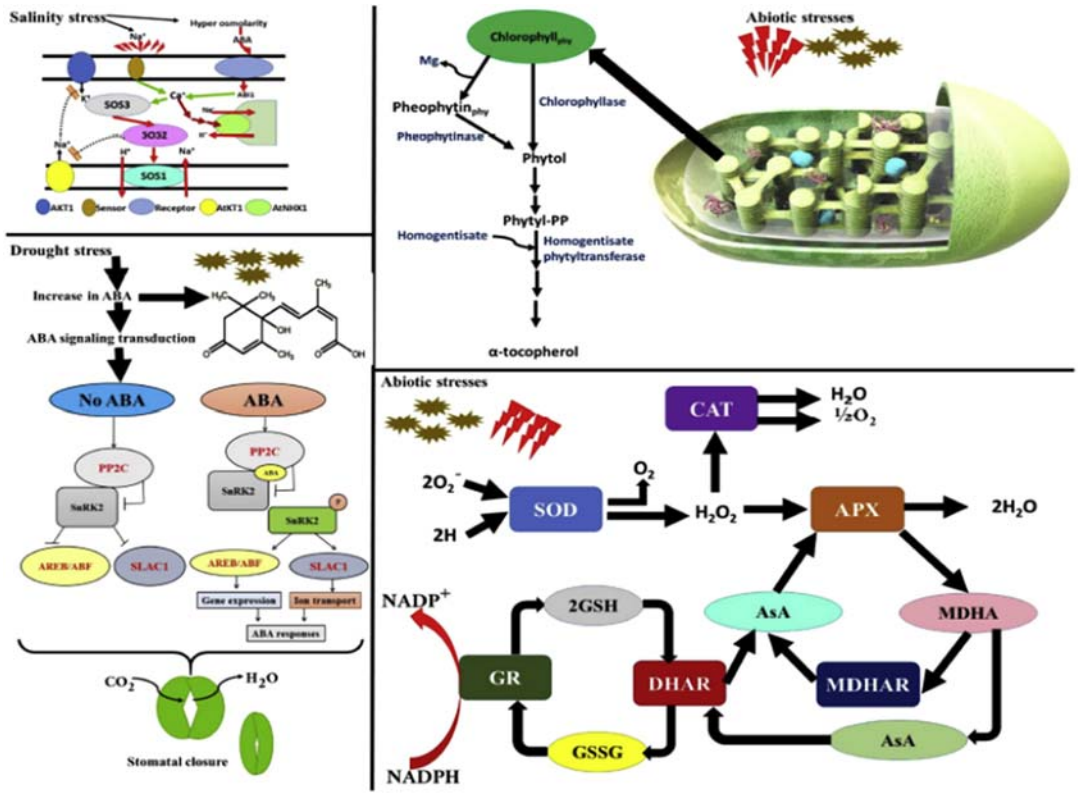

Figure 4.3
Schematic presentation of the underlying pathways that regulate the plant's responses under a stressed environment [12].

Table 4.1: Alleviating effects of nanomaterials (NMs) in plants under different abiotic stresses.

Abiotic stress	Crop	Bionanomaterial	Dose	Beneficial effects	References
Salt stress	Squash (*Cucurbita pepo*)	Nano-SiO_2	—	Enhanced seed germination percentage, H_2O_2, electrolyte leakage, MDA level decreased, reduced the effect of oxidative stress and chlorophyll damage, enhanced levels of antioxidant enzymes, and photosynthetic traits	[93]
	Tomato (*Lycopersicum esculentum* L.)	Nano-SiO_2	25 mM	Increased germination rate, dry mass accumulation, and root length	[99]
	Moringa peregrina	Nano-Fe_3O_4 and nano-ZnO	35, 65, and 95 mg/L	Increased accumulation of K^+, P, N, Fe, Ca^{2+}, Zn, Mg^{2+}, and reduced levels of Na^+ and Cl^-, enhanced the levels of total chlorophyll, crude protein, carotenoids, and antioxidants	[100]
	Basil (*Ocimum basilicum*)	Nano-SiO_2	—	Enhanced fresh and dry mass accumulation, proline, and chlorophyll content	[92]

Continued

Table 4.1: Alleviating effects of nanomaterials (NMs) in plants under different abiotic stresses.—cont'd

Abiotic stress	Crop	Bionanomaterial	Dose	Beneficial effects	References
	Tomato (*Solanum lycopersicum*)	Nano-SiO_2	—	Differential expression of salt responsive genes, upregulated and downregulated to suppress the effect of salt stress and also on the root length seed germination and fresh weight	[101]
	Sunflower (*Helianthus annuus*)	Nano-ZnO	4 g/L	Increased level of proline content, and some antioxidative enzymes	[102]
	Sunflower (*Helianthus annuus* L.)	ZnO	3 g/L	Enhancement of CO_2 assimilation rate, chlorophyll fluorescence, Zn, and reduced Na^+ ions in the leaves	[102]
Flood stress	Soybean (*Glycine max*)	Nano-Ag		Enhanced seedling growth, and stress-related proteins, and reduced production of by-products of the glycolytic pathway	[103]
	Crocus sativus	Ag	30, 60, or 90 ppm	Root growth promoted, and ethylene signaling blocked	[104]
	Soybean (*Glycine max*)	Nano-Al_2O_3		Energy metabolism is regulated, and improved growth	[103]
Drought stress	Basil (*Ocimum basilicum* L.)	TiO_2	0%, 0.01%, and 0.03%	Increased resistance toward the harmful effects of stress	[105]

Continued

Table 4.1: Alleviating effects of nanomaterials (NMs) in plants under different abiotic stresses.—cont'd

Abiotic stress	Crop	Bionanomaterial	Dose	Beneficial effects	References
	Flax (*Linum usitatissimum* L.)	Nano-TiO_2	0, 10, 100, and 500 mg/L	Decreased MDA and H_2O_2 level, increased flax growth, carotenoids, chlorophyll content, and yield	[106]
	Wheat (*Triticum aestivum* L.)	Nano-TiO_2	0.01%, 0.02%, and 0.03%	Enhanced gluten content, starch content, and yield traits	[95]
	Sorghum (*Sorghum bicolor*)	Silicon	—	Increase in leaf, root, and shoot dry weight, chlorophyll (SPAD), and specific leaf weight (SLW)	[107]
	Soybean (*Glycine max* L.)	ZnO	1.0 and 1.5 g/L	Enhanced seed germination characteristics, and reduction of fresh and dry weight	[108]
	Arabidopsis thaliana	Nano-zerovalent Fe	—	Increased accumulation of plant biomass, chlorophyll content, and CO_2 assimilation and activation of stomatal opening	[109]
	Hawthorns (*Crataegus* sp.)	SiO_2	0, 10, 50, and 100 mg/L	Increased MDA content, water potential, plant biomass, and relative water content	[89]
	Crataegus sp.	SiO_2	100, 150 and 200 mg/L	Activation and up-regulation of stomatal conductance, plant biomass, and total chlorophyll content	[89]

Continued

Table 4.1: Alleviating effects of nanomaterials (NMs) in plants under different abiotic stresses.—cont'd

Abiotic stress	Crop	Bionanomaterial	Dose	Beneficial effects	References
	Cotton (*Gossypium* sp.)	SiO_2 and TiO_2	20, 60, 120 ppm) or SiO_2 (100, 200, and 400 ppm)	Enhanced content of total sugars, polyphenolics, reducing power, proline content, activities of antioxidative enzymes (catalase, peroxidase)	[110]

The use of different silica NPs increases plants' resistance to water stress in Hawthorns (*Crataegus* species); the morphological and biochemical behaviors in hawthorn seedlings vary from moderate to severe stress rates in silicon NPs [89]. The positive effects have been reported on photosynthesis, MDA, relative water content (RWC), electrolyte leakage, chlorophyll content, carotenoids, carbohydrates, and proline contents. The role of silicon NPs in preserving essential physiological and biochemical features may be resistant to drought, but the exact mechanism has yet to be grasped [89]. Silicon was used in two sorghum cultivars with different susceptibility to drought with a reduced root (S/R) ratio that showed increased root growth or the preservation of photosynthetic efficiency, regardless of their vulnerability to drought [90]. SiO_2 added into the vegetable medium will decrease the binding capacity of the cell wall of leaf cells, resulting in a reduction in lipid peroxidation. SiO_2 could also shield the cell wall from drought and thermal stress [91]. The application of silica NPs under stress conditions would lead to an increased proline level [92]. The implementation of nano-Si triggered a substantial increase in CAT and POX activities in leaves of Si-treated plants compared with the untreated plants of tomato [93] and alfalfa [94]. Silicon NPs also demonstrate their effect on moisture and translocalization of water and increase the pressure of the turgor, which increases the relative leaf water content and the efficiency of water utilization in pants. Rutile treatment (TiO_2) has resulted in increased germination, dry weight, growth levels, seed vigor, chlorophyll synthesis, ribulose bisphosphate carboxylase (RuBiSCo), oxygenase activities, and chloroplast oxygen estimation speed and facilitated photosynthesis [94]. TiO_2 NPs have increased the growth of wheat plants and their yield under water-deficit stresses [95], controlling enzyme activities that include the metabolization of nitrogen, such as nitrate reductase (NiR), glutamate dehydrogenase (GDH), glutamine synthase (GOGAT), and glutamic pyruvic transaminase (GPT), which assists the plants in the absorption of nitrate

from soil. The foliar spray of ZnO NPs will improve the percentage of germination and germination in soybean compared with water stresses. Nanozinc oxide use was suggested to minimize seed residue's fresh and dry weight during drought stress, showing that zinc NPs were successful in the seed reservoir accumulation and increased tolerance to drought [96]. An experimental finding has shown a substantial effect on plant features such as immense size, the seed count per bollard, the weight of 1000 seeds, and the likelihood of the yield at 1% of iron NPs under dry stress. The foliar spray of iron NPs on Goldasht safflower genotypes displayed the ameliorating effects of improved oil percentage and yield. The use of iron NPs has also increased the growth components at two developmental stages of flora. In contrast, seed formation was enhanced at the flowering stage, as opposed to drought conditions without foliar application of iron NPs [97]. The advancements in the use of AgNPs may be attributed to reducing the loss of plant growth and production by mediating water stress [98].

Iron plays a vital role in plant development and production; its deficiencies contribute to essential changes in the metabolism of the plants and cause chlorosis. Therefore, elements absorbing microelements (iron) may assign a necessary function in drought resistance in plants under drought stress. Several studies have shown that micronutrient application is used to reduce the effects of drought stress and salinity stress. A study showed that iron NPs under drought stress in plants significantly impact traits such as bolls for each branch, seeds for each bollard for thousands of seeds, and a probability of yield of 1%. Fe NPs also increase outputs and returns at different flowering and granule formation stages, but compared with drought without iron NPs, they were better than forming seeds [97]. The reduction of the harmful impact of drought stress on wheat with titanium NPs also showed promising results on some agronomic features such as gluten-seeded and wheat starch content. The results showed that 0.02% titanium dioxide NPs were used for a wide range of agricultural characteristics, including plant height, ear weight, ear size, seed number, the weight of 1000 seeds, ultimate yield, biomass, and harvest indexes with gluten and amid drought stress [95].

4.2 Bionanoparticles under salinity

During growth and development, plants regularly encounter unfavorable environmental conditions, which affect their growth and metabolism [111,112]. Salinity can harm plant production, development, and even survival by applying osmotic stress and nutrient imbalances. The use of additional nutrients, such as calcium, can be used to reduce the responses of ionic imbalance and plant nutritional deficiency in salty soils (Fig. 4.3) and improve the effects of the application of silicone in plants grown in saline soils [113].

Salinity is the scientist's primary concern for sustainable crop production; over 20% of the cultivated land in the world is estimated to suffer from salinity stress, and the sum is

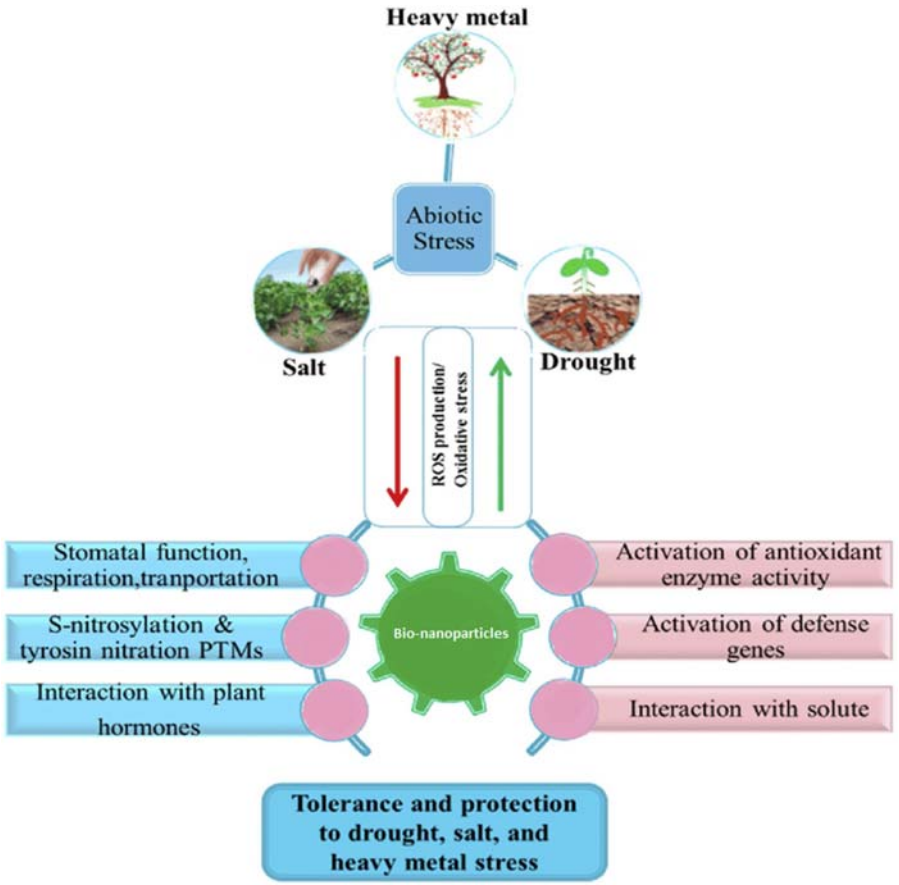

Figure 4.4
Bionanomaterials and their potential role in drought and salinity stress mitigation.

growing day by day [114]. The intensity of salinity harms numerous biochemical and physiological processes linked to plant growth and yield (Fig. 4.4). Reducing the soil osmotic capacity, developing nutritional imbalances, improving different ionic stresses, or one or more combinations of these factors is a common consequence of plant salinity stress [115]. The use of nanofertilizers may represent a potential solution to tackle soil toxicity and other related stress issues. The physiological and biochemical effects on the vegetative attributes were beneficial effects on basil (*Ocimum basilicum*) to high salinity. The results revealed that under salinity, growth indexes, proline content, and total chlorophyll in basil were increased markedly when treated with silicon NPs and silicon fertilizers [92]. SiO_2 NPs display possible increases in chlorophyll size, fresh-leaf weight, dry leaf weight, proline accumulation, and upregulated salinity activity of antioxidant enzymes [99]. Substantial increases in seed germination and seedling growth were observed by administration of SiO_2 NPs in lentils (*Lens culinarium*) under high salinity.

In contrast, a substantial decrease in germination rate and seedling growth was observed in untreated plants. The introduction of SiO_2 NPs promotes the germination rate and fresh weight and increases specific associated lens genotype characteristics under salinity stress. Consequently, SiO_2 NPs strengthen various plant defenses against salt toxicity [116]. Other studies indicated that nano-SiO_2 would increase the fresh weight under salt stress [117]. One approach to reducing the adverse effects of high salinity in the plants is using silica NPs to minimize Na^+ ion accumulation, likely through growing the plant tissue's Na^+ ion absorption [118]. Since salinity is a primary effect of reduced osmotic potential and disturbance of ion homeostasis, Na^+ ion toxicity in plant development significanlty affects the plant growth and develpoment. The reduced length of the root of the plants, such as carrot (*Daucus carota*), cucumber (*Cucumis sativus*), and soybeans (*Glycine max*) in pure alumina, without alteration, is theoretically delayed in plant growth [119].

Salinity is a significant abiotic element in stress. It reduces food production and worsens rising food demand [30,46]. Salinity is the scientific community's fundamental concern for achieving sustainable crop growth. Over 20% of the cultivated land worldwide is projected to suffer from stress on salinity and rising day after day [120,121]. Salinity stress has a detrimental effect on various processes associated with plant growth and biochemical and physiological development (Fig. 4.5). The decrease in osmotic potential, the generation of

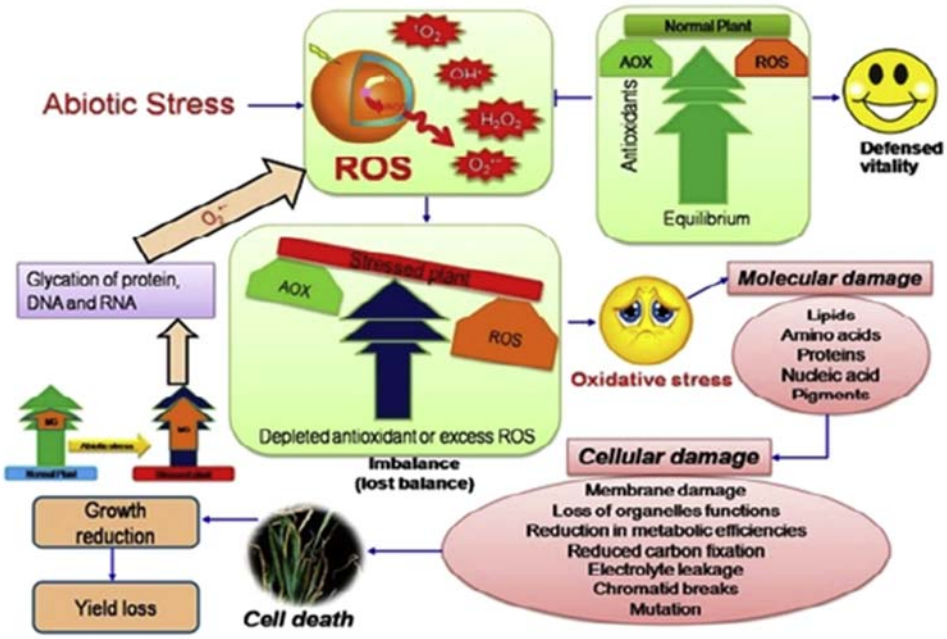

Figure 4.5
An overview of biochemical and physiological changes during salt stress.

food imbalances, and the increase in ion toxicity, and a cumulative effect of other factors are the combined effects of the plant's response to salt stress [115]. Plant salinity stress severely affects some of the other essential processes such as photosynthesis, protein synthesis, and lipid metabolism [122].

5. Environmental and safety issues

It should be recognized very well that NMs may be toxic in their bulk counterpart, particularly in an open farm environment, because of their increased contact region (Fig. 4.6) [123,124]. For instance, there are solid matrices with NMs that are free to add a nanostructure to their surface. They can moderately be expected to release or leach when they are in contact with water and air or subjected to mechanical forces reasonably foreseeable [125].

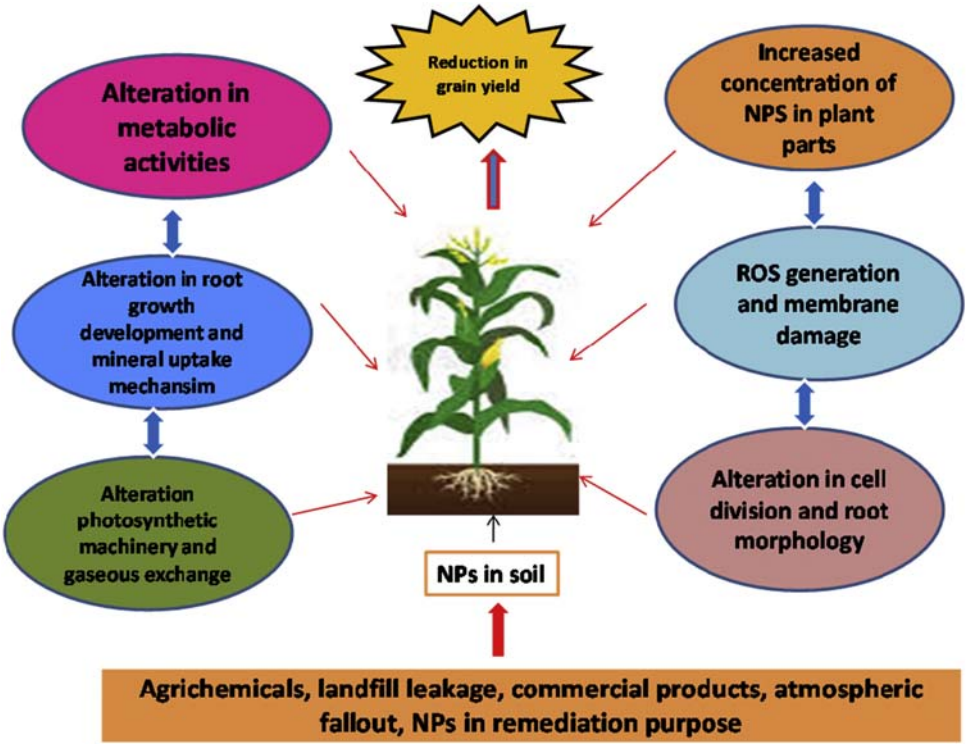
Reduction in grain yield
Alteration in metabolic activities
Increased concentration of NPS in plant parts
Alteration in root growth development and mineral uptake mechansim
ROS generation and membrane damage
Alteration photosynthetic machinery and gaseous exchange
Alteration in cell division and root morphology
NPs in soil
Agrichemicals, landfill leakage, commercial products, atmospheric fallout, NPs in remediation purpose

Figure 4.6

Possible sources of soil nanoparticles and their effect on plant growth and physiology. Different activities by plants, such as alteration in the root, shoot, development, physiology, and metabolic processes of the entire plant decrease the yield and quality under the stress of nanoparticles.

NMs have far-reaching implications for both the general public and the environment. However, without knowledge of the necessary qualities, the extent of the preventive actions that must be taken is unknown. It is critical to embrace the life cycle perspective to grasp the possible impact of any NM on the environment. This involves assessing the effects that may occur throughout an item's life cycle, including manufacturing, circulation, handling, use, storage, and disposal. According to the US Department of Energy's (DOE 2007) Guidance for the Transfer of Hazardous Materials and the UK Environment Agency's (EA) Guidance for the Transfer of Hazardous Materials, a plan for storing and disposing of NMs or NMs contaminated waste should be devised, taking into account the hazardous nature of the materials and the quantities included and associated with NM-bearing waste streams (solid and fluid waste).

The current challenges are that the available tools for surveying NMP security are frequently unsuitable or so difficult to use that adequate assessment of the safety of these materials and advances remains extremely dangerous, and the assets or testing instruments are not capable of enabling security assessment of the novel NMs that are flooding the market. This means that to resolve this issue, completely new safety evaluation criteria will need to be developed in the future. Thus, there is a need for a quick assessment of research requirements and the development of a road map for strengthening the safety of NMs and nanotechnologies in the future. As a result, a variety of groups must work together, ranging from academic institutions to health institutions, governmental organizations, independent research institutes, and for-profit corporations. Associations/organizations having a clear stake in nanotechnology should participate to a reduced extent, but it should not be the major emphasis.

6. Future perspective

Nanotechnology is rapidly growing, and innovative technology in a wide range of industries and other sectors. Nanotechnology and NPs applications in sustainable agriculture and crop enhancement remain, however, in the early stages. Therefore, it has become essential to understand specific relationships of NPs with plants, both at the cellular and molecular levels, to allow the use of the peculiar and unique features of NPs in the agricultural industry to exploit their potential benefits. In addition, the accumulation of NPs in the system and its effects to prevent possible adverse effects on the environment must be evaluated, given the increased application of nanotechnology in an industry that leads to the environment. There are not many reports on the phytotoxicity of NPs on the plants available so far. Therefore, it is crucial to understand the interaction between plants and NPs and the size and concentration optimization of NPs before practical use in the fields to reduce their potential adverse effect on natural ecosystems and crops.

Future research should concentrate on the interaction of NPs with signaling pathways that result in a shift in defense enzyme gene expression. Furthermore, there are currently significant restrictions to utilizing costly NPs in agriculture. Treatment using GNPs and AgNPs is not cost-effective. Understanding the mechanism by which these NPs modulate plant immunity may thus aid in the development of a new strategy for improving plant tolerance. Because of changing climatic circumstances, soil types, plants to be treated, and, most significantly, the physicochemical character of metallic/nonmetallic NPs, many of the manufactured NPs are still limited in their field use. Toxicity and NP buildup in agricultural plants are two limitations related to field applications. Future research on the toxicological effects of nanotechnology on model microorganisms, plants, and animals will be critical for deploying nanotechnology in the field.

NPs have been shown to help with salinity, heavy metal, and drought in a number of investigations. However, further research into the multiple therapies' synergistic effects is required before solid conclusions can be drawn. Long-term research on cereal crops and other important crops is also recommended to show the link between NPs dosage, soil types, and ecological effects. When assessing the toxicological impact of NPs on various creatures and ecosystems before implementing their potential advantages, caution is required.

7. Conclusion

Nanotechnology is in its early stages in agriculture, also at a global level. Nanoscience develops a range of low-cost nanotechnology interventions for increased crop production, biotic and abiotic stresses. The NPs enhance the stress tolerance mechanism in plants by enhanced water absorption and root conductance with differential protein expression, which is positively correlated with oxidation−reduction reactions, ROS detoxification, stress, hormonal pathways, and boost stress tolerance. The interaction of NPs with cells and tissues may lead to plant proteomics and transcriptomic pathways that eventually affect plant growth and development. An extensive analysis of growth, characterization, biodegradability, ecological design, and potential applications and NPs' potential applications and translocations will require further investigations of their potential role in agriculture.

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SECTION 3

Biomedical applications

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CHAPTER 5

Emerging applications of bionanomaterials in medicine and drug delivery

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Abbreviations

5-FU	5-fluorouracil
AA	Acrylic acid
ASP	Angelica sinensis polysaccharide
BNC	Bacterial nanocellulose
BSA	Bovine serum albumin
BsAb	Bispecific antibody
CDs	Carbon dots
CNCs	Cellulose nanocrystals
CUR	Curcumin
DDD	Drug-delivering-drug
DOC	Docetaxal
DOX	Doxorubicin
DSF	Disulfiram
EGPR	Epidermal growth factor receptor
EPMO	Ethane bridged periodic mesoporous organ silica
FB	Flurbiprofen
GNPs	Gold nanoparticles
GO	Graphene oxide
HCDs	Hollow CDs
HER	Human epidermal growth factor receptor
HPMC	Hydroxy propyl methyl cellulose
IB	Inclusion bodies
IBU	Ibuprofen
LDLBNPs	Low density lipoprotein bionanoparticles
LDLR	Low density lipoprotein receptor
MDR	Multidrug resistance
MPS	Mononuclear phagocyte systems
ND	Nanodiamonds
NS	Nanosuspensions
O-MWNTs	Oxidized multi-walled carbon nanotubes
PCT	Paclitaxel

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PDT	Photodynamic therapy
PEG	polyethylene glycol
PG	Polyglycerol
PVA	Polyvinyl alcohol
RES	Reticuloendothelial system
SLNs	Solid lipid nanoparticles
SSOs	Splice-shifting oligonucleotide
Tf	Transferrin
TGF-β1	Transforming growth factor β1
TMX	Tamoxifen
VEGF	Vascular endothelial growth factor

1. Introduction

The existing scientific period is of nanotechnology which has roots of chemistry with stem of engineering and branches of biology. It demonstrates enormous potentials in the field of medicine as nanodrug and nano carriers [1]. Bio-nanotechnology has emerged as permutation amongst biotechnology and nanotechnology for rising biological synthesis and environmental-benign technology for synthesis of nanomaterials. The usage of nanoparticles is fast enticement in the present century as they posses' distinct chemical, optical and mechanical properties. Along with them, the metallic nanoparticles are utmost promising as they contain amazing antibacterial possession sowing to their large surface area to volume ratio, which is of consideration to scientists due to the increasing microbial resistance in contrast to metal ions, antibiotics, and the development of resistant strains [2,3]. The applications of nanomaterial's to biology or medicine or agriculture are drug and gene delivery, biosciences, fluorescent biological labels, tumor destruction via heating (hyperthermia), probing of DNA structure, bio-detection of pathogens, detection of proteins, MRI contrast enhancement, Pago kinetic studies, tissue engineering, separation and purification of biological molecules and cells, anti insect molecules and antimicrobials [4].

Bionanomaterials are nanotechnology-empower biomaterials. Widespread research has been eager to the progression in the field of bionanomaterials for an innumerable of biomedical applications together with challenging cancers [1−4]. Bionanomaterials recommend assurance to afford resolutions to the complex complications related with cancer treatment, moreover, to provide better capacity and efficiency in cancer cell extermination. Bionanomaterials are prepared by using biocompatible nanomaterials, for passive and active targeting techniques, hyperthermic strategies, and several added mechanisms to target tumors [5]. Nano drug delivery systems can target the drug to particular site of body, evade side effects, overawed solubility problems and toxicity and be personalized to have the proper immunogenicity and metabolic stability. Still with the use of rational design principles, promising a drug delivery platform regularly count on

synthesizing and showing a library of drug results to find a suitable candidate [6–8]. The greatest imperative property of nanoparticles is their larger surface area per unit volume, which increases the rate of mass transfer, mostly at elevated temperatures [9]. Functionalization of nanomaterial makes it potential to attain the preferred properties and attach various compounds to the nanomaterial. Nanomedicine is a promising field implementing the use of understanding and techniques of nanoscience in medical biology and disease prevention and remediation. It implicates the utilization of nanodimensional materials including nano robots, nano sensors for diagnosis, delivery, and sensory purposes, and actuates materials in live cells (Fig. 5.1) [10].

Thus Bionanotechnology offer multiple benefits in treating chronic human diseases by site-specific and target-oriented delivery of medicines. Though, insufficient knowledge about nanostructures toxicity is a major concern and undoubtedly warrants additional research to improve the efficacy with higher safety to enable safer practical accomplishment of these medicines. Bionanotechnology offers the finest possibility concluded the progress of nanostructured materials and nanoparticles able to progress the efficiency of molecular virulence modulators and novel antimicrobial compounds and to confirm their targeted delivery and controlled release [11]. Targeted drug delivery is a favored method for drug administration that increase the concentration of the drug at the preferred sites of action, while leaving other tissues of the body unaffected [12]. Since of their small sizes, nanoparticles are capable to penetrate inflammatory sites, tumors or microcapillaries. They are also capable to cross the blood-brain barrier unlike other drug delivery systems with bigger sizes [13]. The small size also allows a high cellular uptake

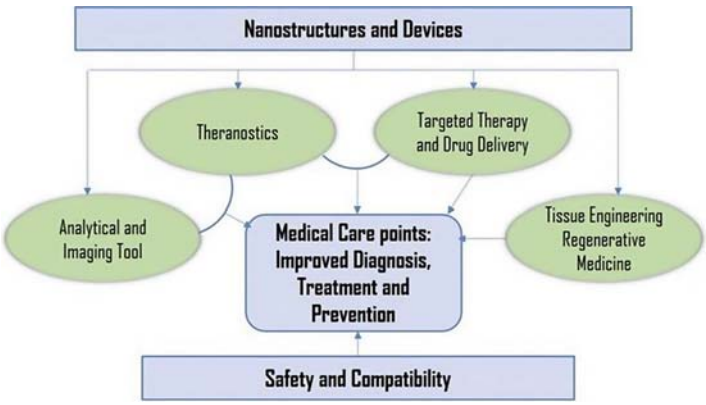
Nanostructures and Devices
Theranostics
Targeted Therapy and Drug Delivery
Analytical and Imaging Tool
Medical Care points: Improved Diagnosis, Treatment and Prevention
Tissue Engineering Regenerative Medicine
Safety and Compatibility

Figure 5.1

Application and goals of nanomedicine in different sphere of biomedical research [10]. *This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. You are not required to obtain permission to reuse this article. CC0 applies for supplementary material related to this article and attribution is not required.*

by a variety of cell types. The design of drug delivery systems, nanoparticles are loaded with drugs and specificity is achieve by conjugation with a ligand that solely binds to diseased cells. Interactions with healthy tissue should be hampered. Therefore, the advantages of a targeted drug delivery system are reduction of adverse effects in combination with increased efficacy [14]. This chapter intended to present the various emerging applications of bionanomaterials in medicine and drug delivery field.

2. Inorganic bionanomaterials

2.1 Metal nanoparticles and metal oxide nanoparticles

Multifunctional metal nanoparticles present exceptional opportunities for medical advancement like drug delivery, cellular imaging, biomedical diagnostics and therapeutics as of their small sizes and unique properties [15]. Plasmonic nanoparticles are particularly helpful for numerous biomedical applications subsequently of their improved resonant absorption and scattering properties, in addition to strong Raman scattering which are essential properties for their applications in PDT, optical imaging, and Raman probe design [16]. GNPs are examples of smart candidates for such applications owing to small sizes, ease of preparation and bioconjugation, strong absorbing and scattering properties in addition to their well-known biocompatibility. GNPs have exposed the exploit in delivery of peptides, proteins, or nucleic acids like DNA or RNA. Non-covalent DNA-GNP conjugates offer an efficient means of delivery in mammalian 293T cells [17]. GNPs could probably be employing in delivery of diatomic therapeutic agents like singlet oxygen or nitric oxide. Singlet oxygen, a cytotoxic species involves in PDT of cancer [18]. Elechiguerra et al. developed silver nanoparticles in a size range 1−10 nm bound with HIV-1 in a size dependent approach. They reported that silver nanoparticles inhibit HIV-1 infection in CD4+MT-2 cells and cMAGI HIV-1 reporter cells. Bare silver nanoparticles exhibited greater effect, while surface modification with BSA and PVP showed moderate effect [19]. Medicinal use of bare platinum nanoparticles is unusual. Platinum nanoparticles have been used in combination with other nanoparticles, either in the form of an alloy, or core-shell or bimetallic nanoclusters. Yolk-shell nanocrystals of FePt@CoS_2 have been observed to be additional potent in killing HeLa cells compared to cisplatin. The IC_{50} value of FePt@CoS_2 was an initiate to be 35.5 ± 4.7 ng of Pt/mL for HeLa cells, but, it was 230 ng of Pt/mL in case of cisplatin [20]. Bunschoten A et al., was studied Ac-TZ14011-HSA-Ag nanoparticles for their ability to bind to human breast carcinoma cells (MDA-MB-231) over expressing a GFP-tagged version of the human CXCR4 receptor. The fluorescence signal of GFP (500−600 nm) was used as reference readout for the target receptor. Tumor cells treated with nonfunctional zed HSA-Ag nanoparticles did not illustrate binding of the nanoparticles to the cell membrane. Tumor cells incubated with Ac-TZ14011-HSA-Ag nanoparticles exposed clear co-localization between the GFP signal

and the emission of the Ag nanoclusters. The overlap in signal on the cell membrane established binding of Ac-TZ14011- HSA-Ag nanoparticles to the CXCR4-receptor and therefore provides proof that functionalized Ag Nano clusters may be used in targeted applications [21]. Hessel et al. reported that CuSe NPs can be energized using 980 nm light and destroy a human colorectal cell line, however at the same time retaining a desirable size for long circulation. Moreover, they reported that CuSe NPs also have a better thermal efficiency when compared to both Au NRs and Au NPs [22]. Furthermore Kale et al. developed monodispersed, super paramagnetic nickel cobaltite (NCO) nanoparticles then functionalized using mercaptopropionic acid (MPA). MPA conjugates with NCO forming a metal-carboxylate linkage, with the MPA-MPA interaction up via configuration of disulfide bonds, leaving another carboxyl end free for extra conjugation. The cytotoxicity studies on NCO-MPA demonstrated cell viability of ~100% up to a dosage of 40 μg/mL on SiHa, MCF7, and B16F10 cell lines, and on mouse primary fibroblasts. Negligible leaching (b5 ppm) of ionic Co or Ni was noted into the delivery medium. Ahead subjecting the NCO-MPA dispersion (0.1 mg/mL) to radiofrequency absorption, the nanoparticles were heated to 75°C within 2 min, suggestive of its assure as a magnetic hyperthermia agent. Moreover, the amino acid lysine and the drug cephalexin were effectively adducted to the NCO system, suggesting its potential for drug delivery [23].

2.2 Other inorganic bionanomaterials

For the last few years, major accomplishments have been devoted to surface modification of various nanoparticles and imaging agent carriers such as iron oxide nanoparticles, polymeric nanoparticles, liposomes, quantum dots, polymeric micelles, and viruses to target them particularly to preferred cells and tissues. Specifically targeted delivery systems for tumor cells are highly attractive to enhance therapeutic and diagnostic efficacy with reducing uninvited side effects. Targeting ligands together with peptides, antibodies, carbohydrates, and aptamers, which exclusively bind to the receptors over expressed only in cancer cells, have been commonly tethered on the surface of nanocarriers to deliver them to the tumor tissue in a more precise manner. Therefore, numerous scientists developed nanoparticles and explored to treatment of various diseases [24]. For examples Mok et al. reported that pH sensitive polymer coatings might effectively be removed from both quantum dots and gene bearing adenoviruses, ensuing in a positive surface charge which exhibited superior accumulation in cells. pH induced gel shrinkage has also been use for selective imaging using Ag NPs [24]. Luo et al. showed incorporating magnetic NPs with a pH responsive polymer which dissolved in acidic environments. Here imaging and therapy could be gained concurrently with specific localization. Even with these capable results, though, it has been noted lately that many polymeric systems are restricted by a lack of sensitivity to small changes in physiological pH. The dispute of synthesizing

highly selective pH responsive polymers is essential for advancing pH induced drug delivery with polymer−NP composites [25]. Meng et al. have confirmed the effective co-delivery of doxorubicin and siRNA to combat multi drug resistant cancer using a mesoporous silica NP containing carboxylate and phosphonate functional groups for electrostatic stabilization. In acidic conditions such as the cell lysosome, the stabilization interaction is diminished and the drug can diffuse into the cell [26]. Lately, Zhang et al. reported that hollow mesoporous silica nanoshells with included magnetic nanoparticles can transport doxorubicin bound during amide functionality, with the corresponding release at lower pH. A similar strategy has been engaged for the release of bound doxorubicin from Au NPs utilizing a carbamate linkage [27]. Zink et al. has used changes in pH to open molecular valves on the surface of mesoporous silicate NPs to release hydrophobic drugs, with valve components with cucurbit [6] uril, pseudorotaxanes and cyclodextrin [28]. Cheng et al. synthesized asymmetric lollipop-like mesoporous silica nanoparticles of Fe_3O_4@SiO_2&EPMO consisting of core-shell structured Fe_3O_4@SiO_2 nanospheres and EPMO. The asymmetric nanocomposite shows the efficient for cancer cell killing and bacteria inhibition. Fig. 5.2 shows the uptake of nanoparticles loaded with dual-drugs within the MCF-7 cells using confocal laser scanning microscopy (CLSM). The cell nuclei were labeled by DAPI (blue fluorescence) and Cur showed green auto fluorescence. After incubating the cells from 0.5 to 12 h, the green fluorescence intensity gradually increased in the cell cytoplasm, indicating that more Fe_3O_4@ SiO_2-GS&EPMO-Cur had been effectively taken up by MCF-7 cells. After 12 h, Fe_3O_4@SiO_2-GS&EPMO-Cur was mostly located in the cell cytoplasm and no considerable emission of green fluorescence was an experiential in the cell nucleus [29].

2.3 Carbon bionanomaterials

2.3.1 Nanodiamonds

NDs are carbon-based materials broadly recognized candidates for biomedical applications owing to their excellent biocompatibility, bright photoluminescence based on color centers and wonderful photo stability [30]. The emission band position of NDs depends only on the defect structure. The peak in the emission from NDs is in the blue-green range which is not best for imaging of live cells. The brightest emission from ND, conversely, occurs in the green-red range depending on the structure of the defects produced in the ND core. The fluorescence intensity strongly increases with ND size, as larger size encompasses additional color defects. One mostly advantageous aspect regarding ND photoluminescence when it comes to biomedical applications is that the nitrogen-vacancy defect centers emit photons in the far-red/near-infrared region that professionally penetrates tissue while being well separated from tissue and cellular auto fluorescence. The current trend in the design of new nanomedicine involves nanoparticulate formulations that can combine drug delivery and imaging to allow for instant diagnostics

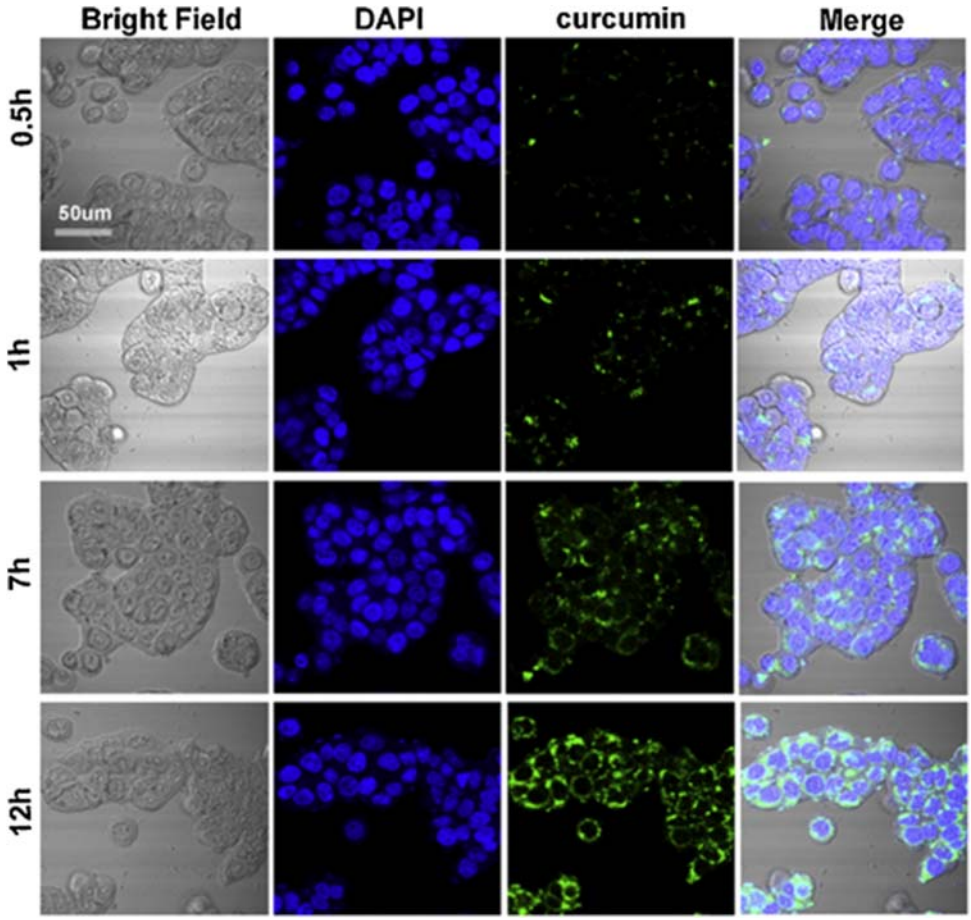

Figure 5.2

Confocal laser scanning microscopy (CLSM) observations of the MCF-7cells after incubation with Fe_3O_4@SiO_2-GS&EPMO-Cur for 0.5, 1, 7, and 12 h. *From Copyright 2020, Elsevier Y. Cheng, Y. Zhang, W. Deng, J. Hu, Antibacterial and anticancer activities of asymmetric lollipop-like mesoporous silica nanoparticles loaded with CUR and gentamicin sulfate, Colloids Surf., A B186 (2020) 110744.*

and therapy, often referred to as theranostics. Whereas this can be realized via many fabrication designs, one particularly gorgeous approach is the building of core/shell materials where one construct is accountable for the imaging activity and the other for the drug incorporation [30]. Recently, Ho and co-workers introduced ND as a potential nanomedical drug delivery platform [31]. Moore et al. prepared NDLPs that were functionalized with antibody to target the EGFR on implanted MDAMB-231 (triple negative breast cancer) cells and tumors in mice while also delivering the epirubicin chemotherapeutic which led to marked improvement in treatment efficacy and development of chemotherapeutic tolerance. Moreover, the scalability, chemical stability

and biocompatibility also prove that NDLPs are a promising future chemotherapeutic delivery vehicle [32]. Xi et al. studied the employ of convection-enhanced delivery (CED) to administer the NDs adsorbed with DOX as a potential drug delivery system [33]. They found that the drug distribution and maintenance improved when ND was complexes with DOX in contrast to the other formulas. *In vivo*, ND–DOX prohibited cell growth and induced cell dose to a greater degree than unmodified DOX over time, additional supporting the biocompatibility of NDs [33,34]. Nanodiamonds coated with polymers exhibits the biocompatibility, resistance to degradation in a cellular environment, and hydrophilicity. For examples, the polymers used in NDs consist of PEG and PG (Fig. 5.3). Like other nanoparticles, PEG has been used to coat NDs. Conversely, the hydroxyl groups in the PEG side chain have the propensity to undergo enzyme-catalyzed oxidation to aldehydes under in vivo conditions, and these aldehydes are possible to additional react with proteins. As well, the PEG coating is not sufficient to disperse the NDs in cellular media and to suppress nonspecific protein adsorption. Thus, PEG-coated NDs are now used in combination with BSA in bio applications. A chic direct way to solve this problem is to use hyper blanched HPG, which can cover NDs more densely than the linear chain PEG. HPG are more hydrophilic than PEG and are less disposed to oxidation or thermal

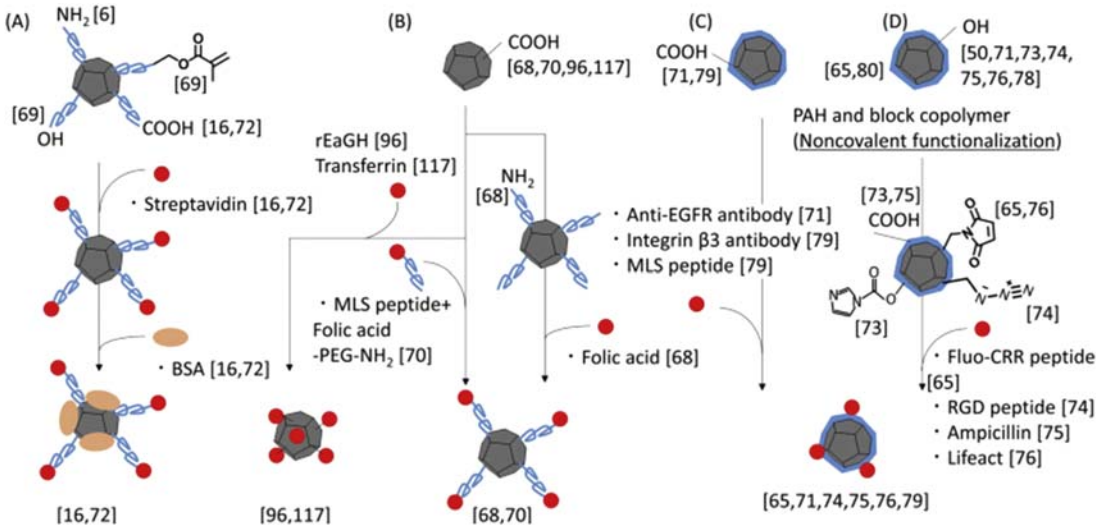

Figure 5.3

Polymer-coated NDs for specific targeting using (A) a combination of linear polymer and proteins, (B) linear polymer or direct conjugation approach (C) HPG or HPG-COOH coating method, and (D) HPG, block copolymer or PAH coating method. Red circle: Biomolecules to specifically recognize the proteins of interest (such as antibodies, peptides, sugar chains, and biotin-avidin systems). *From Copyright 2020, Elsevier D. Teradaa, T. Genjoa, T.F. Segawa, R. Igarashic, M. Shirakawa, Nanodiamonds for bioapplications—specific targeting strategies, Biochim. Biophys. Acta Gen. Subj. 1864 (2) (2020) 129354.*

stress than the hydroxyl groups in PEG. The HPG coating layer can be controlled by the reaction time; very thin layers (∼5 nm) were reported in the case of 30-nm NDs. Furthermore, the HPG layer does not influence the optical properties of fluorescent NDs (Fig. 5.3) [35].

2.3.2 Fluorescence carbon dots

Fluorescence CDs with a size smaller than 10 nm, outstanding biocompatibility, low to none cytoxicity, high quantum yield, non-blinking, and low cost are measured as a rising star in Nanomedicine [36]. Though, in terms of emission tunability, the control over the emission of CDs is still in progress with improved understanding of the interplay between the surface states and intrinsic states in photoluminescence. Currently developments have yielded in simple synthesis of highly green emitting CDs and red-emitting CDs, which qualify CDs as an in vivo bioimaging agent and drug delivery system [37]. Zeng et al. synthesized green-emitting CDs by a simple one-step microwave synthesis into a DDS that discriminate cancer cells from normal cells by loading DOX. Zing et al. carried out in vivo studies and confirmed that the carboxyl-rich green-emitting CDs are a nontoxic bioimaging agent for drug biodistribution, and an in vivo study showing that the CDs can be used as a stable cancer DDS that can selectively kill cancer cells performing localized therapy due to their finite size and rich surface chemistry for forming non-covalent bonds with drug payloads [38]. Yuan et al. applied CDs for anticancer drug delivery using DOX as the model chemotherapeutic drug, with a revelation to improving the therapeutic efficiency of DOX. The CD-DOX complexes were shown improved therapeutic efficiency in using the L929 mouse fibroblast cell line and the ACC-2 adenoid cystic carcinoma cell line. Fig. 5.4 shows confocal fluorescence images of ACC-2 cells that had been incubated with CDs (300 μg/mL), free DOX (3.5 μM), and CD-DOX for 4 h. CDs were mainly located in the cytoplasm with a smaller quantity visible in the nucleus. Free DOX was located both in the nucleus and cytoplasm but was primarily concentrated at the nuclear membranes. Especially, the CD-DOX complexes showed distinct nuclear localization, which was in contrast to the CDs and free DOX. This targeted delivery to the nucleus is important to maximize the therapeutic impact of DOX in an antitumor approach, as DOX needs to reach the nucleus to exert its impact [39].

Wang et al. developed hollow CDs (HCDs) from BSA by solvothermal reaction. The HCDs are used as a delivery system for DOX. The DOX-HCD drug delivery system showed pH-controlled release, and is quickly taken up by cells. Since of their exact nanostructure and photoluminescence properties, the multifunctional HCDs prepared here show potential for application in both cell imaging and cancer therapy [40]. Lai et al. carried out on drug delivery using C-dots and obtain excellent optical properties of C-dots by conjugating $mSiO_2$-PEG to the surface of the dots. The $mSiO_2$-PEG-C-dots were employed as a drug carrier for the anticancer drug DOX in HeLa cells [41].

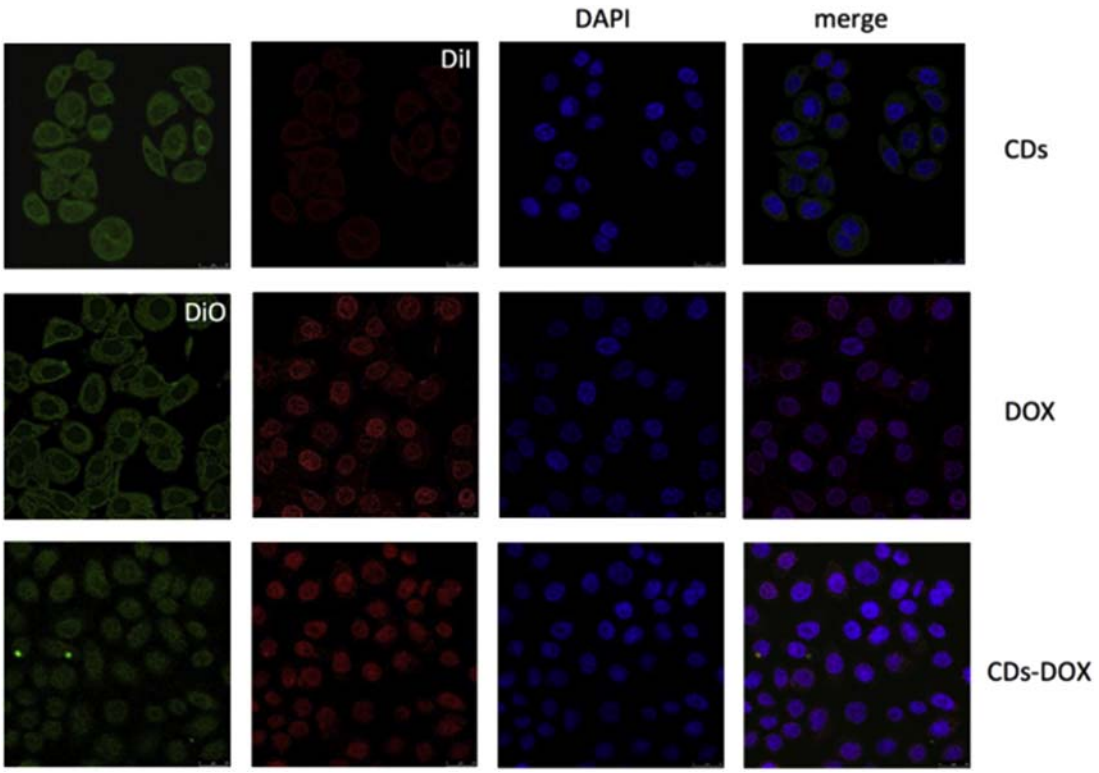

Figure 5.4
Shows confocal fluorescence images of ACC-2 cells that had been incubated with CDs (300 μg/mL), free DOX (3.5 μM), and CD-DOX (at the same concentration of DOX) for 4 h. *From Copyright 2017, Elsevier Y. Yuan, B. Guo, L. Hao, N. Liu, Y. Lin, W. Guo, B. Gu, Doxorubicin-loaded environmentally friendly carbon dots as a novel drug delivery system for nucleus targeted cancer therapy, Colloids Surf., B 159 (2017) 349–359.*

Mewada et al. designed C-dots from sorbitol and further passivated them with BSA, which enhanced the drug-loading capacity and biocompatibility. DOX was loaded on the surface of BSA-C-dots with an 86% drug loading capacity. At pH 7.2, this complex displayed 12% drug release. The BSA-C-dots killed more cancer cells than did the free BSA [42]. Recently, Wang et al. fabricated DOX-conjugated beer C-dots (BC-dots) exerted a prolonged drug release profile toward MCF-7 cells. Laser scanning confocal microscopy established the internalization of BC-dots-DOX in MCF-7 cells. *In vitro* analysis of BC-dots-DDS showed bioimaging function and anticancer activity with excellent biocompatibility [43].

2.3.3 Nanotubes

Nanotubes are promising attractive carriers in drug delivery applications. Due to their attractive propertyand extraordinary functions of natural tubular structures applied in

different fields such as molecular separation and transport, catalysis, optics, electronics, chemotherapy and drug delivery. In these contexts, nanotubes have been made of zeolites, graphite, inorganic complexes, lipids and cyclodextrins [44]. Zhang et al. have reported the release of doxorubicin from carbon nanotubes modified with carboxylate groups and coated with polysaccharides, noting that the loading efficiency and release rate can be controlled by carefully tuning the surface properties [45]. Faria M et al., explored the titanium oxide nanotubes (TiO_2) for the development of therapeutic devices and imaging probes for nanomedicine. They studied the surface modification of TiO_2 nanotubes with ZnS quantum dots and were found to produce a red shift in the ultra violet emission band. Also Faria M et al., studied that the biocompatibility against mammalian cells (Chinese Hamster Ovarian Cells—CHO) suggesting that TiO_2/ZnS may also have suitable optical properties for use as biological markers in diagnostic medicine. The drug release characteristic of TiO_2/ZnS nanotubes was explored using 5-FU an anticancer drug used in PDT. The results show that the TiO_2/ZnS nanotubes are a promising candidate for anticancer DDS. Fig. 5.5 reveals the presence of hybrid TiO_2/ZnS nanotubes within the cellular cytoplasm throughout a characteristic ZnS yellow fluorescence. This result indicate that the hybrid TiO_2/ZnS nanotubes formed in this study seem to show suitable optical properties for use as a marker of biological cells [46].

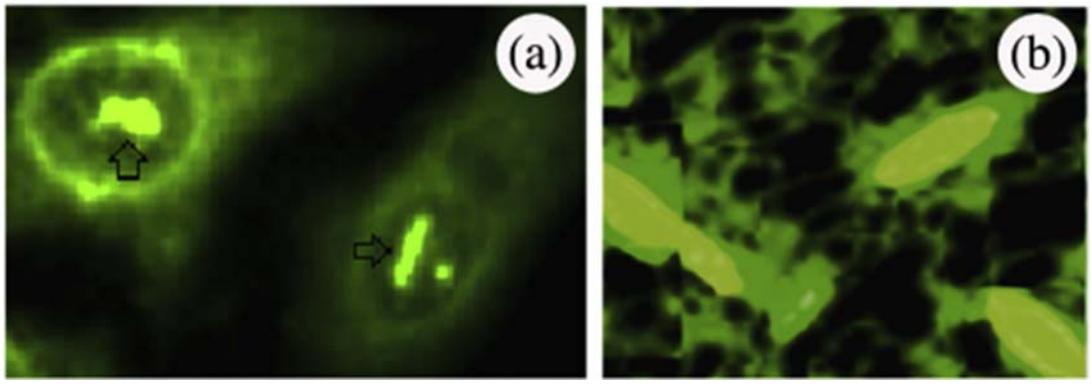

Figure 5.5

Confocal micrographs of cultured sycamore cells after 2 h incubation in a medium containing the TiO_2/ZnS nanotubes. The volume of 0.1 mL of a suspension of TiO_2/ZnS nanotubes at concentration of 0.1 mg/mL was added to 1 mL of the sycamore cells suspension (1.0×10^4 cells/mL). The *arrows* in (A) indicate the presence of TiO_2/ZnS nanotube aggregates. The yellow fluorescence in (B) appears after excitation at 300 nm and corresponds to TiO_2/ZnS aggregates of nanotubes present at cytosol. *From Copyright 2015, Elsevier H. Antonio, M. Faria, A. Antonio, A. Queirozm, A novel drug delivery of 5-fluorouracil device based on TiO_2/ZnS nanotubes, Mater. Sci. Eng. C56 (2015) 260–268.*

Ren et al. developed a dual-targeting drug delivery system based on PEGylated O-MWNTs modified with angiopep-2 (O-MWNTs-PEG-ANG) for treatment of brain glioma. Ren et al. stated that MWNTs can not only distribute in brains but, also accumulate in tumors, and have ultrahigh surface area with extraordinarily high loading anticancer drug of DOX, which was selected as drug carrier. The supportive dual-targeting to brain glioma by O-MWNTsPEG-ANG was evaluated by intracellular tracking in vitro and fluorescence imaging in vivo, which confirmed that the combination of O-MWNTs-PEG and angiopep-2 constituted an ideal dual targeting DDS. The anti-glioma effect of DOX-loaded O-MWNTs-PEG-ANG (DOX-OMWNTs-PEG-ANG) was assessed by C6 cytotoxicity and median survival time of glioma bearing mice, which showed a better anti-glioma effect than DOX. Finally they confirmed that O-MWNTs-PEG-ANG is a capable dual-targeting carrier to deliver DOX for the treatment of brain tumor. Fig. 5.6, exhibited the fluorescent distribution of FITC-O-MWNTsPEG-ANG and FITC-O-MWNTs-PEG in BCEC cells (Fig. 5.6A) and C6 cells (Fig. 5.6B). Angiopep-2 has been used as ligand for brain targeting delivery, or dual-targeting to brain glioma, since it is a high-efficiency ligand to LRP receptor and LRP receptor is over expressed on the BBB and glioma cells. Considerably higher uptakes of O-MWNTs-PEG-ANG than O-MWNTs-PEG by BCEC and C6 cells were displayed in this study (Fig. 5.6), mostly owing to the interaction of angiopep and LRP receptor [47].

2.3.4 Graphene

Graphene group contains various materials, including graphene, graphdiyne, graphane, GO, reduced GO (rGO), graphene quantum dots, etc. Intended for biomedical application, materials should be similarity and safe. Graphene group materials were initially introduced in biomedical field as high-performance vectors for anticancer drug delivery, and researchers found that graphene family materials possess extremely high drug loading capacity, which were greater than any other materials that have been ever developed [48]. As well, by loading on graphene-based carriers, the intrinsic defects of free drugs, including nonspecific targeting, short blood circulation time, and fast elimination through metabolic cycle, could be effectively overcome. To more progress the drug delivery performance, surface modification of the carriers is widely used. For instance polymers with good biocompatibility were adopted to increase the stability of graphene-based carriers in physiological condition, molecules with target recognition function are used to progress the active-targeting performance of graphene-based carriers to pathological tissues, whereas substances with exogenous or endogenous stimuli-responsive properties are utilized to add controllable and smart drug release concert [49]. Jafari et al. synthesized nanocomposite hydrogel beads of chitosan/TPP/GO (CS/TPP/GO) with different weight% (0−20%wt) of GO using physical interactions between CS hydrogel and GO nanosheets and evaluated for the first time as pH -sensitive intelligent drug delivery system with high loading capacity, acceptable mechanical strength, and antibacterial and

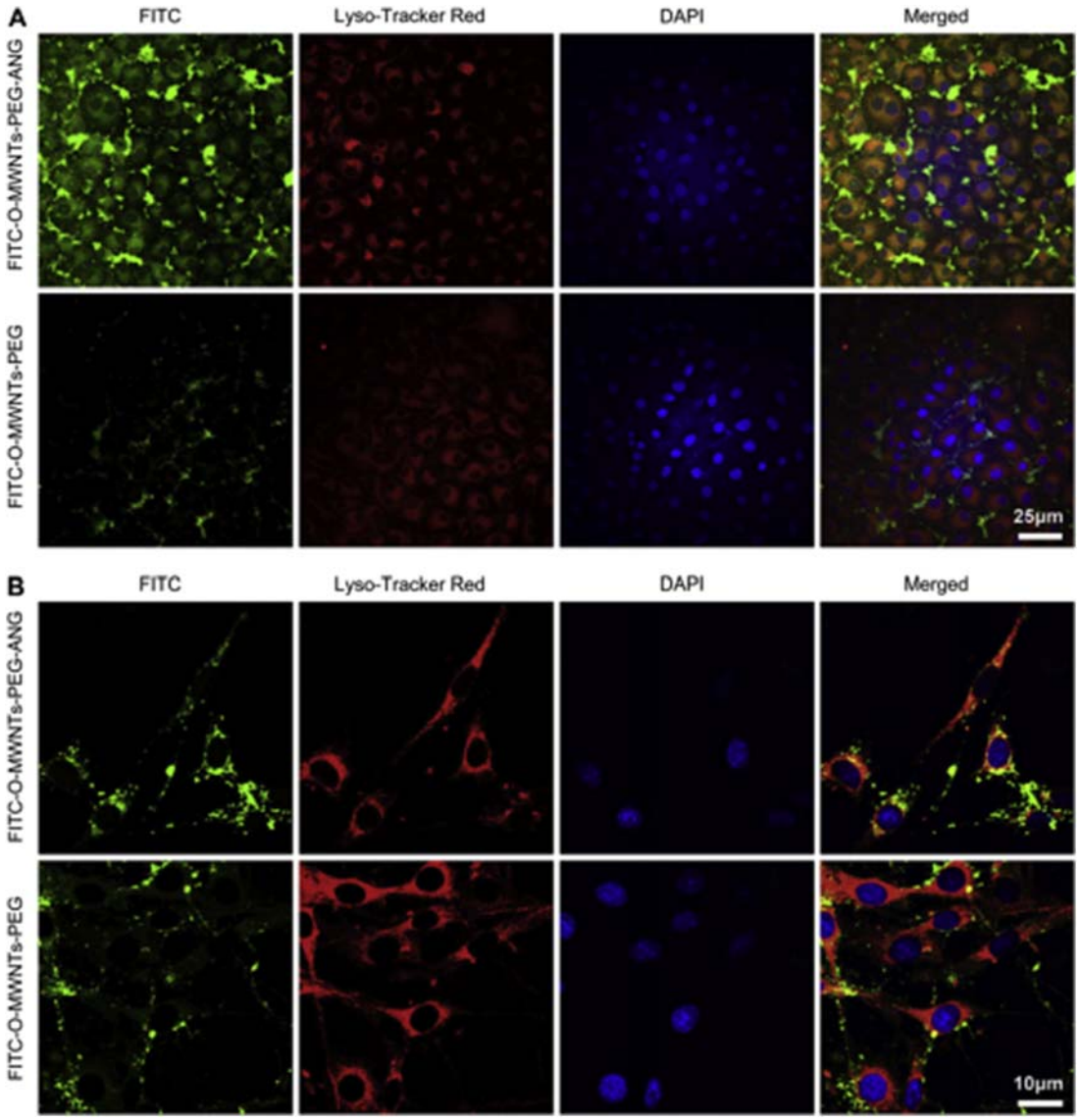

Figure 5.6

Intracellular fluorescence distribution in BCEC cells (A) and C6 cells (B) after incubated with FITC-O-MWNTs-PEG or FITC-O-MWNTs-PEG-ANG (containing 10 μg/mL, FITC) for 2 h, the nuclei were stained with DAPI and the lysosomes were stained with Lyso-tracker red. Images were obtained under FV1000 confocal laser scanning microscopy. *From Copyright 2012, Elsevier J. Ren, S. Shen, D. Wang, Z. Xi, L. Guo, X. Pang, Y. Qian, X. Sun, X. Jiang, The targeted delivery of anticancer drugs to brain glioma by PEGylated oxidized multi-walled carbon nanotubes modified with angiopep-2, Biomater. 33 (2012) 3324–3333.*

non-toxic properties. The controlled release of the drug from the hydrogels was investigated [50]. Yang et al., *prepared* GO−DOX hydrochloride nanohybrid (GO−DOX) via a simple noncovalent method, and the loading and release behaviors of DOX on GO were investigated. The release behavior of the water-soluble anticancer DOX and found that in acidic medium (pH 2) the release of the drug was more than 70% after a time period of 30 h which was 4 times greater than in a medium with pH seven or 10 and therefore this drug with GO will give a higher drug release at acidic pH compared with other pH [51]. Li et al., fabricated Janus-chorded mesoporous silica nanoparticles (UCNP−SiO_2−$mSiO_2$−PMO) containing a hydrophilic domain of UCNP−SiO_2−$mSiO_2$ in contrast to the hydrophobic domain of PMO. The efficient co-loading of hydrophobic PCT and hydrophilic DOX have been furnished on UCNP−SiO_2−$mSiO_2$−PMO and consequently targeted against malignant cells. Moreover, the authors engineered a Janus-nanostructured surface with thermo responsive 1-tetradecanol and photosensitive azobenzene in order to convert normal drug release to smart release with the aforesaid stimuli. Interestingly, the drugs from the combination exposed more tumoricidal efficiency (∼50%) compared to their individual formulations (∼25%) [52]. Xie et al. developed magnetic graphene oxide and non-covalently functionalization of GO via layer-by- layer (LbL) to deposition of chitosan and sodium alginate on functionalized magnetic graphene oxide nanocomposites for modification of magnetic GO so that its stability and dispersibility under physiological conditions could be enhanced whereas maintaining its high loading capacity, magnetism and cell uptake (Fig. 5.7). The results of the Cellular studies denoted magnetically targeted cellular uptake characteristics and excellent photothermal effect of mGO-CS/SA, as well as concentration-dependent cytotoxicity of mGO-CS/SA-DOX. Finally Xie et al. reported that mGOCS/SA can be consider as proper candidates for application in targeted drug delivery and PDT [53].

2.4 Polymeric bionanomaterials

2.4.1 Dendrimers

Dendrimers are the focused macromolecules which deal regular and extremely branched three-dimensional structures. Their exclusive structures show high density of functionalities at the periphery of the molecules. For example, dendrimers with peripheral amines permit capable condensation of negatively charged nucleic acids, while the tertiary amines in the core remain accessible for playing an important role during endo/lysosomal acidification which enables more proficient endosomal release. A dendrimer is normally symmetric around the core. Its structure provides comparatively simple contact to control their size, composition, and chemical reactivity very exactly. The degree of branching is articulated in the form of generation of the dendrimers. The size and surface charge on dendrimers differ with the number of “generations” during synthesis [54]. As of the presence of large number of tertiary amines, PAMAM dendrimers act not only as proton

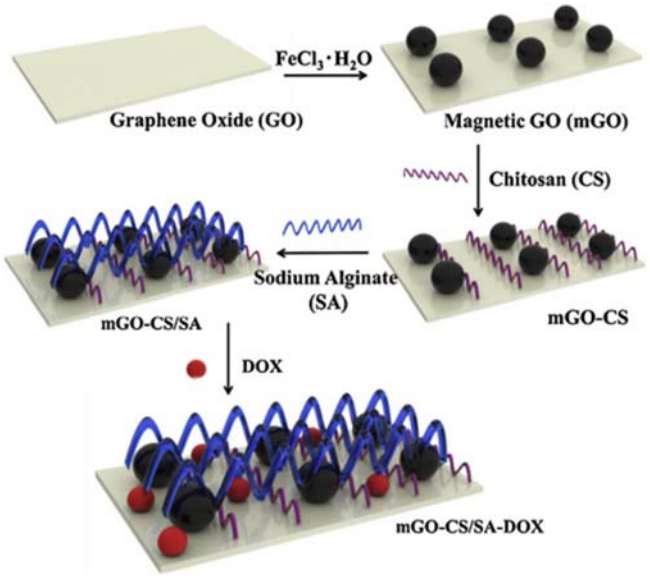

Figure 5.7
Depiction of the synthesis of mGO-CS/SA and DOX loading. *From Copyright 2019, Elsevier M. Xie, F. Zhang, H. Peng, Y. Zhang, Y. Li, Y. Xu, J. Xie, Layer-by-layer modification of magnetic graphene oxide by chitosan and sodium alginate with enhanced dispersibility for targeted drug delivery and photothermal therapy, Colloids Surf., B 176 (2019) 462–470.*

sponges in gene delivery however, also along with carbon skeleton, they have been used as drug carriers an instantaneously [55,56]. Haensler and Szoka reported for the first time the use of PAMAM dendrimers in gene delivery. They exhibited that the sixth generation dendrimer was approximately 10-folds superior than lower generation ones. Based on their study, PAMAM dendrimers have lately been used in several in vivo and in vitro gene delivery applications and found to be biocompatible [57]. Madaan et al. reported PAMAM dendrimers have a distinct size and shape however offer limited flexibility. Hence, attempts have been made to hydrolytically cleave some of the amide bonds in the inner part. Breakings of some of the branches of dendrimers in the core enhance the flexibility and the resulting molecules are known as activated dendrimers. Though activated and inactivated dendrimers were found to form complexes with DNA by electrostatic interactions and act as mediators for transfer of bound DNA into eukaryotic cells. The overall transfection efficiency of activated dendrimers was found to be two to three times higher than the inactivated (native) dendrimers. The fractured or activated dendrimers not only revealed the greater flexibility to interact with plasmid DNA, however their solubility also improved and presented less tendency to aggregate. This superior flexibility of activated dendrimers showed better endosomal release of the DNA and therefore the transfection efficiency [58]. Han et al. prepared an amphiphilic conjugate of PAMAM

dendrimer by conjugating hydrophobic PLA which on self-assembly formed core-shell nanostructures in which 5-FU and doxorubicin were entrapped efficiently for combinatorial anticancer therapy. This system exhibited synergistic antitumor effect on MDA-MB 231 tumor cell line and in MDA-MB 231 xenograft mice model [59]. Gardikis et al. developed new chimeric advanced Drug Delivery nano systems (chi-aDDnSs) as DOX carriers by incorporating two conventional liposomal systems (i.e., DOPC/CHOL and EPC/CHOL); one of which (EPC/CHOL) had the same lipid composition (marketed product "Myocet), was incorporated into the newly synthesized PG1 dendrimer and assessed the in vitro cytotoxicity against human cancer cell lines. Finally, the in vitro activity studies revealed that both liposomal and chi-aDDnSs preparations were able to retain the growth inhibiting activity of the free anthracycline while they diminished the drug toxicity of the drugs against the 2 cell lines tested. Fig. 5.8 shows the toxicity against human breast cancer cell lines MB231 and MCF7 for DOPC/CHOL, DOPC/CHOL/PG1, EPC/CHOL and EPC/CHOL/PG1 at various concentrations up to 100 M and was found to be inactive [60].

2.4.2 Polymeric micelles

Polymeric micelles are formed by the attractive and repulsive forces of surfactant molecules to come close enough to acquire an ordered structure [61]. The driving forces that allow the formation of micellar system is the hydrophobic attraction while ionic repulsion and/or solvation force acts as the opposition force. Concentration of the surfactant is the strength that is requisite to form the first micelle (CMC) [62]. These micelles have widely been used in drug delivery applications. For example, Genexol PL is PTX encapsulated PLA-PEG micelles [63]. Salzano et al. developed, dual stimuli-sensitive mixed polymeric micelles (MM) for co-delivery of the endogenous tumor suppressor miRNA-34a and the chemotherapeutic agent DOX into cancer cells. They performed the MMP2-sensitivity of PEG2k-CLV-DOX conjugate in the tumor mass; by developing MMP2-overexpressing 3D spheroid model of HT1080 cells. Subsequent to the treatment, the fluorescent signal of free DOX in all layers of the spheroids was superior compared to the conjugates, owing to its immediate availability in the system and consequent superior and deeper penetration. Still, the sensitivity of the conjugate to MMP2 cleavage was established by higher and deeper penetration signals after the treatment with PEG2k-CLVDOX compared to the uncleavable control. The PEG chains not detached from the PEG2kUNCLV-DOX conjugate increase hydrophilicity and size of the molecule, which hinders its internalization in the tumor mass. After checking the capability of DOX conjugate to penetrate the tumor mass on its own, the cytotoxicity of the MM was tested in the 3D spheroid model. TAT/miRNA-34a MM had no effect in 5-day old, however, promoted 35% of cytotoxicity in 7-day old spheroids. It has been revealed that the characteristics of 3D multicellular tumor spheroids are subject to their maturity, which can influence response to the treatment. The resulted value was particularly interesting owing

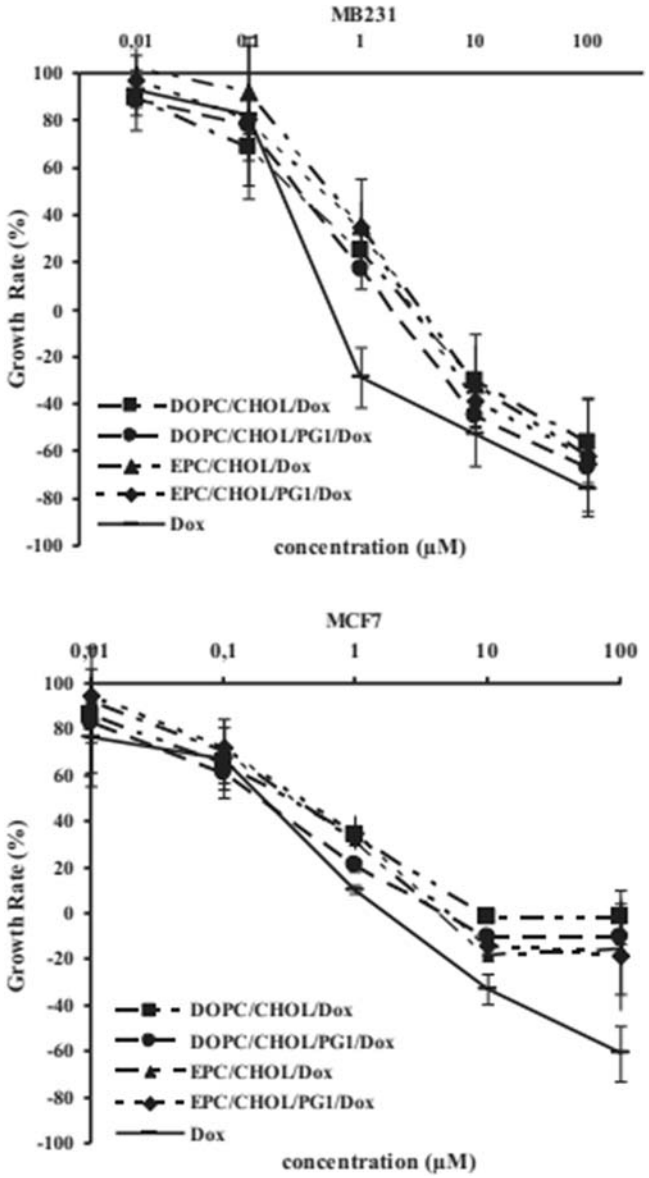

Figure 5.8

Percent growth rate of MB231 and MCF7 human breast cell lines upon treatment with various concentrations of free Dox and the formulations: DOPC/CHOL/DOX, DOPC/CHOL/PG1/DOX, EPC/CHOL/DOX, EPC/CHOL/PG1/DOX for 48 h [60]. *From K. Gardikis, C. Tsimplouli, K. Dimas, M. Micha-Screttas, C. Demetzos, New chimeric advanced Drug Delivery nano Systems (chi-aDDnSs) as doxorubicin carriers, Int. J. Pharm. 402 (1–2) (2010) 231–237. https//doi.org/10.1016/j.ijpharm.2010.10.007.*

to the fact that chemotherapy resistance related to oncogene protein levels are more expressed in matured spheroids. Hence, they suggested that the dual sensitive MM be able to penetrate into the solid tumor mass owing to MMP2-sensitive PEG detachment and release functional miRNA-34a due to GSH-sensitive cleavage of the conjugate inside the cells [64]. Gener et al. reported on the anticancer and anti-metastatic effects of new Zileuton loaded polymeric micelles, using in vivo breast CSCs models. They observed that significant intratumoral reduction of CSCs in vivo, and also a strong reduction of circulating cancer cells and CSCs in the blood in these models. Subsequent to 10 min all cells have internalized the tagged micelles and the intracellular amount of them followed to increase afterward, as it was professed by a constant increase of the fluorescence intensity (Fig. 5.9A). Entertainingly, no significant differences regarding PMs internalization were experiential between the subpopulations of CSCs and non-CSCs, respectively (Fig. 5.9A). By confocal microscopy, they observed lysosomal co-location of PMs tagged with 5-DTAF after 1 h and also 24 h after internalization (Fig. 5.9B) [65].

2.4.3 Polysaccharide nanoparticles

Polysaccharides are the polymers of monosaccharides. In environment, polysaccharides are obtained from algal origin (e.g., alginate), plant origin (e.g., pectin, guar gum), microbial origin (e.g., dextran, xanthan gum), and animal origin (chitosan, chondroitin). Polysaccharides contain a large number of reactive groups, a broad range of molecular weight (MW), an anecdotal chemical composition, which give to their assortment in structure and in property [66]. Due to the presence of assorted derivable groups on molecular chains, polysaccharides can be effortlessly modified chemically and biochemically ensuing in many kinds of polysaccharide derivatives. As natural biomaterials polysaccharides are extremely stable, safe, non-toxic, hydrophilic and biodegradable. In computation, polysaccharides have plentiful resources in nature and low cost in their processing. Predominantly most of natural polysaccharides have hydrophilic groups such as hydroxyl, carboxyl and amino groups, which could form non-covalent bonds with biological tissues (mainly epithelia and mucous membranes), forming bioadhesion [67]. For instance chitosan, starch, alginates and so on are good bioadhesive materials. Nanoparticle carriers prepared of bioadhesive polysaccharides might prolong the residence time and therefore increase the absorbance of loaded drugs. For the application of these natural polysaccharides for drug carriers, issues of safety, toxicity and ease of use are greatly simplified. Currently a large number of studies have been conducted on polysaccharides and their derivatives for their possible application as nanoparticle DDS [68]. Henry Lindemann et al. developed Polysaccharide Nanoparticles bearing histone deacetylase inhibitors (HDAC) Inhibitor as nontoxic nanocarrier for drug Delivery. Thus valproic acid (VPA) is covalently attach to cellulose and dextran via esterification with degree of substitution and studied the cellular uptake using HeLa cells. They investigated the cellular uptake of the VPA-loaded NPs, rhodamine B-labelled NPs (CV2-RB,

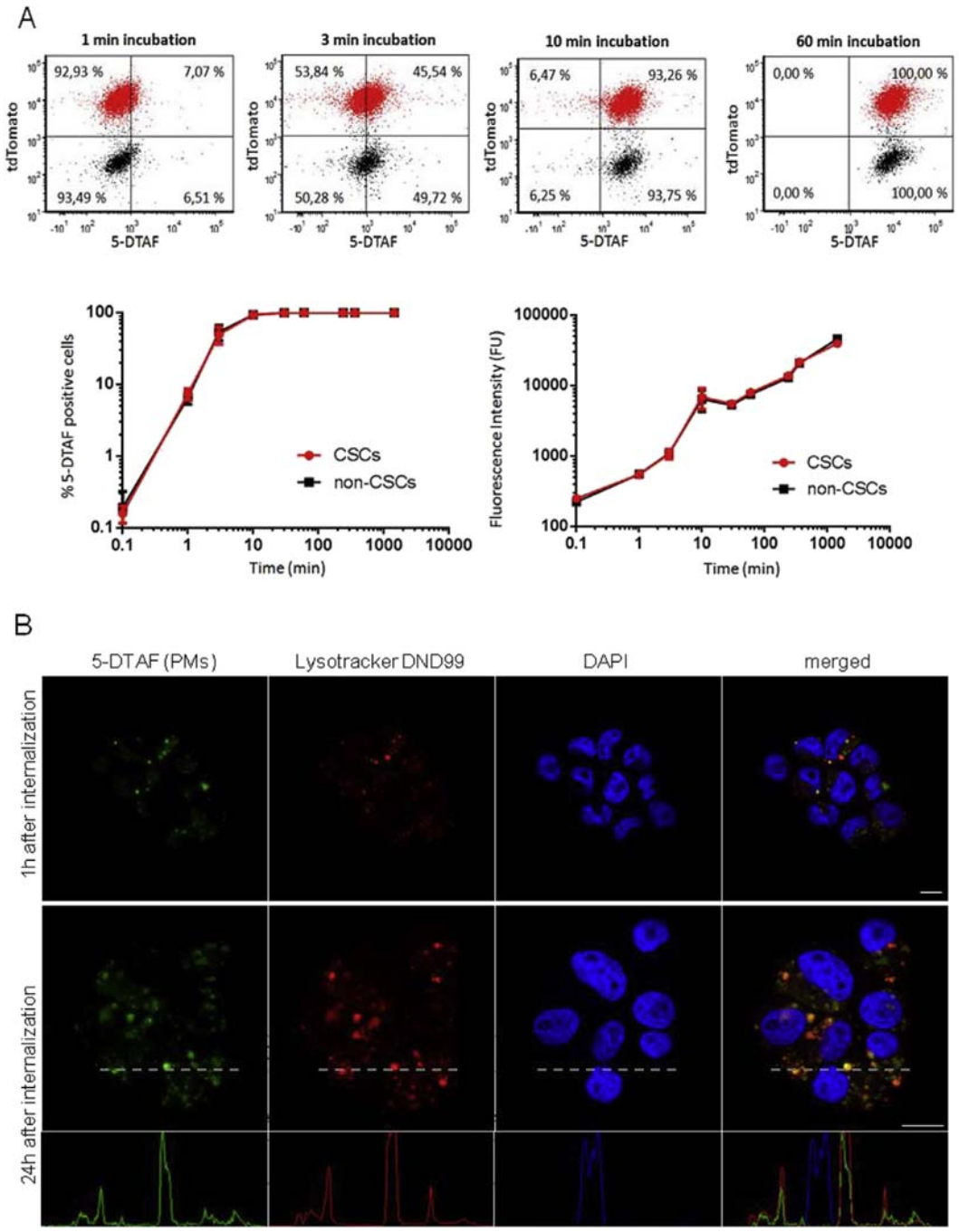

Figure 5.9

Internalization of PM-Zileuton in breast cancer cells. (A) Over time course quantification of CSCs (tdTomato+; red) and non-CSCs (tdTomatoblack) cellular uptake of fluorescently tagged PMs

DV2-RB) and NPs with encapsulated Nile Red were used in live cell imaging studies. Uptake of CV2-RB in HeLa cells occurred within few seconds and the NPs mostly localized in the cytoplasmic compartment, which might be proven by z-stack analysis [69].

Wang et al. studied the possibility of ASP as an intuitive liver targeting drug delivery carrier with applications in acute alcoholic liver damage by conjugating Amphipathic cholesteryl hemisuccinate-ASP (ASP-CHEMS) via desertification reaction and in the in vivo cellular uptake behavior study and in vivo bioimaging experiments [70]. As exposed in Fig. 5.10A, at each time point, the tremendously weak fluorescence signals of free DIR did not exceed the DIR-labeled nanoparticle signals in body circulation. Starting at 0.25 h post injection, a stronger fluorescence signal was found in the liver of the DIR/ACNPs group, even as weaker fluorescence intensity was observed in the antagonist NGA group and DIR/DCNPs group. Earlier addition of the antagonist NGA competitively neutralized the ASGPR receptors, thus delaying the accumulation of DIR/ACNPs in the liver. Furthermore, the strongest fluorescence signals in the liver region were still observed after 24 h in the DIR/ACNPs group, and were distinctly stronger than in the DIR/DCNPs group. In addition, ex vivo fluorescence images (Fig. 5.10B) additional confirmed that DIR/ACNPs exhibited higher fluorescence accumulation in the liver. Thus in vivo bioimaging results indicated that ACNPs had a remarkable liver-targeting capability due to the active mechanism, which was achieved by ASGPR-mediated endocytosis. As shown in Fig. 5.10C and D, free Cur was mainly distributed in the lung and rapidly eliminated after IV administration. ACNPs could promote the accumulation of Cur in the liver and spleen. Though there was a rapid reduce in the Cur content in the liver in the Cur/ACNPs group after the first 1 h, a significantly higher content of Cur was still noted in the liver in the Cur/ACNPs group than in the free Cur group at the same time point after administration, which is consistent with the in vivo result [70].

(PM-DTAF), reported as percentage of DTAF positive cells and relative increase of fluorescence intensity over time. For each sample, at least 10,000 individual cells were collected and the mean fluorescence intensity was evaluated. (B) The internalization of PM-Zileuton in breast MDA-MB-231 cancer cells was also observed by confocal microscopy 1 and 24 h after internalization. Micelles were labeled with 5-DTAF (green fluorescence), lysosomes were labeled with Lysotracker DND99 (in red) and DAPI was used to visualize nuclei (in blue). The co-location of micelles and lysosomes was confirmed by fluorescence intensity plots over the illustrated dot line (24 h). *From Copyright 2020, Elsevier P. Gener, S. Montero, H. Xandri-Monje, Z.V. Díaz-Riascos, D. Rafael, F. Andrade, F. Martínez-Trucharte, P. González, J. Seras-Franzoso, D. Arango, I. Abasolo, J.S. Schwartz, Zileuton™ loaded in polymer micelles effectively reduce breast cancer circulating tumor cells and intratumoral cancer stem cells, Nanomedicine 24 (2020) 102106. https://doi.org/10.1016/j.nano.2019.102106.*

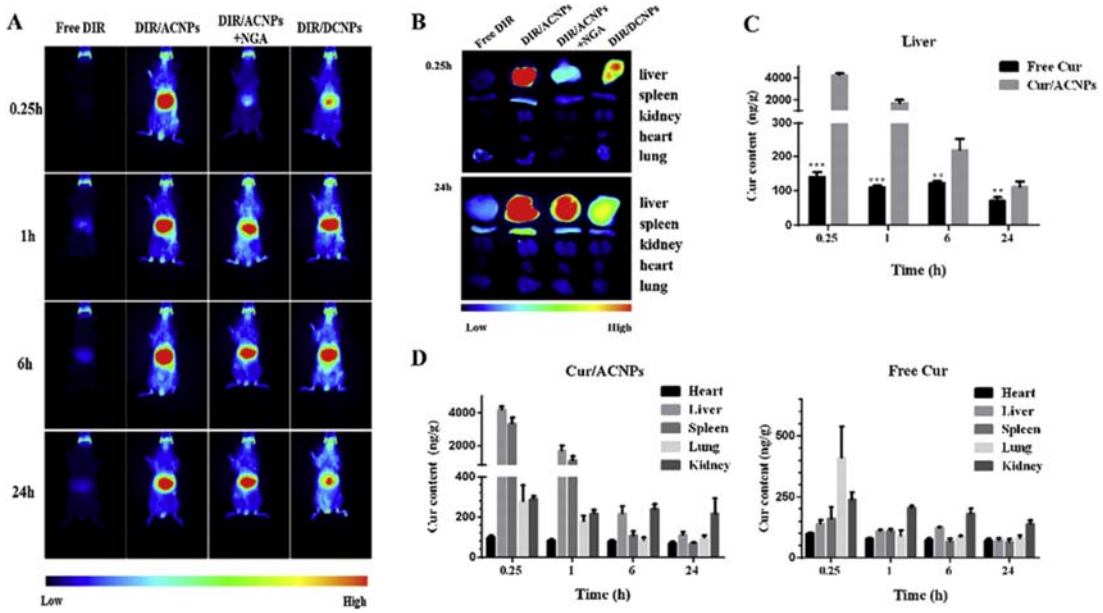

Figure 5.10

Bioimaging and tissue distribution. (A) *In vivo* DIR fluorescence images of female BALB/c mice obtained at different time points with different DIR formulations. (B) *Ex vivo* imaging of the isolated organs at 0.25 and 24 h post-injection. (C) Distribution of Cur in the liver at 0.25, 1, 6 and 24 h after intravenous administration of Cur/ACNPs and free Cur solution. (D) The tissue distribution of Cur/ACNPs and free Cur in mice at 0.25, 1, 6 and 24 h after intravenous administration, respectively. *From Copyright 2020, Elsevier K. Wang, J. Xu, Y. Liu, Z. Cui, Z. He, Z. Zheng, X. Huang, Y. Zhang, Self-assembled Angelica sinensis polysaccharide nanoparticles with an instinctive liver-targeting ability as a drug carrier for acute alcoholic liver damage protection, Int. J. Pharm. 577 (2020) 118996.*

2.4.4 Hydrogels

Hydrogel are the bionanoparticles serve as unique building blocks for constructing three-dimensional (3D) bio-functional hydrogels owing to their monodispersity in size and shape, genetic and chemical addressability of multivalent exterior surface, in addition to good biocompatibility. Stimuli-responsive hydrogels have revealed immense possible for controlled drug release, sensing, 3D cell culture and tissue regeneration applications [71]. Chen et al. developed supramolecular hydrogel by simple mixing of β-CD-modified M13 (M13-β-CD) with Azo-modified HA (HA-Azo and investigated the possible of the M13-β-CD/HA-Azo hydrogel as a 3D cell culture and release system by encapsulating MC3T3-E1 cells in *insitu* formed hydrogel [71]. Badshah et al. evaluated BNC matrixes as drug carrier for famotidine and tizanidine. Famotidine is poorly and the tizanidine highly water soluble, respectively. Both drugs were homogeneously loaded and distributed into

the matrixes. Around 80% of tizanidine (hydrophobic) was released by the cellulose matrix within 15 min, whereas commercial tablets took at least 3 times longer. For tinizanidine both delivery systems reached 80% of release in 15 min [72]. Treesuppharet al. developed a hydrogel composite synthesized by copolymerization of BNC with gelatin. Both size and shape of BNC chains were homogeneous and hydrogel existing thermal stability, chemical resistance and preferred mechanical properties. The rate of the hydrogel swelling was expected to range from 400% to 600%. A few extra studies stated the appropriateness of nanocellulose hydrogels applied to drug delivery [73]. Cairu et al. investigated the synthesis and characterization of a bacterial nanocellulose-AA hydrogel for drug delivery. AA monomers were grafted onto cellulose fibers and the gelification activated and accelerated by electron-beam irradiation [74]. Evaluation of water absorption exhibited that BNC-AA hydrogel reached its maximum swelling at pH 7, even after 48 h. At pH 10, the equilibrium was achieved in 24 h. This mechanism relies on the hydrophilicity of the carboxylic groups of the hydrogel structure. Fig. 5.11, Showed that the gel pore size was reliant upon the content and the irradiation dose in a relative manner. In addition, the gel porosity directly affected the kinetics of drug releasing [74].

Ahlen et al. have established in vitro sustained release of pilocarpine hydrochloride (PL) from poloxamer (PM) modified CNC with enhanced rheological and overall properties for ocular drug delivery. Ahlen et al. disclosed that the transport phenomenon of all the PM

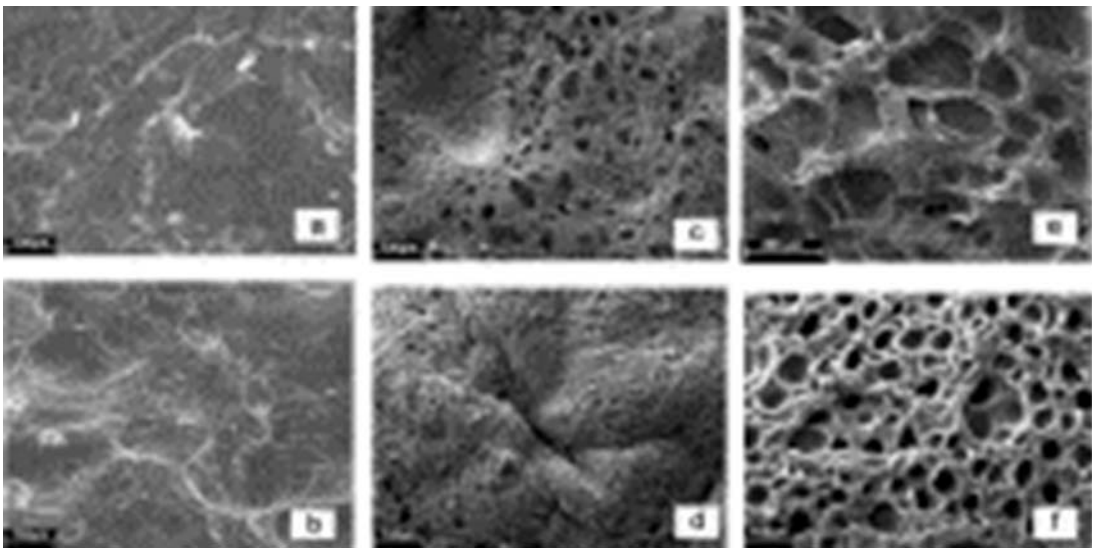

Figure 5.11

Scanning electron microscopy images of thermo- and pH-responsive poly (acrylic) acid-bacterial nanocellulose hydrogel applied to drug delivery. *From Copyright 2012, Elsevier M. Cairul, M.I. Amin, N. Ahmad, N. Halib, S. Ahmad, Synthesis and characterization of thermo- and pH-responsive bacterial cellulose/acrylic acid hydrogels for drug delivery, Carbohydr. Polym. 88 (2) (2012) 465–473.*

and its nanocomposite hydrogels was anomalous transport while the critical gelation concentration of PM reduced from 18% (w/v) to 16.6% (w/v) with the adding of different CNC% (w/v). They, furthermore show from their report that the adding of different CNC% (w/v) in PM for the engineered nanocomposite hydrogels led to excellent sustained release of the PL up to more than 20 h [75]. Zubik et al. reported that thermo-responsive hydrogels containing poly (N-isopropyl acrylamide) (PNIPAAM), reinforced with CNC by means of both covalent and non-covalent interactions with it. The hydrogels performed well and showed decent drug-loading capacity at ambient temperature and a burst drug release, which was followed by slow and sustained release at 37°C [76]. Wafaa et al. developed nanoparticle loaded hydrogel based contact lenses and explored its potential for the ocular drug delivery. A drug prolong release over 28 h' period was experiential after inclusion of the nanoparticles in the composite lenses. They revealed from their study that the nanoparticles−CNC−PVA lenses showed even greater potential for extended drug release, which they attributed to the particles leaching from the swelling PVA-network during the incubation period [77].

2.4.5 Nanocellulose

With the anticipation for designing new drug-delivery systems, the development of abundant, natural, biodegradable, and biocompatible polymers has involved great interest because the discovery of nanocellulose(NCs) [78,79]. Owing to their excellent properties (nanoscale size, high specific aspect ratio, biodegradability, sustainability, good mechanical strength, and low toxicity) and their composites have an engrossed increasing research interest and been widely explored for various applications, especially in biomedical fields. In comparison to other nanomaterials, the NCs have more extraordinary advantages such as simple accumulation in tumor tissue, penetrating tumor microenvironment, and improved cell uptake [79]. Kim et al. were developed surface-modified CNCs for proficient delivery of polymeric siRNA in cancer cells. Cationic CNCs were synthesized using the hydrothermal desulfation and chemical modification method (Fig. 5.12). Primary, CNCs were hydrothermally desulfated to control the desulfation degree for improving the aqueous dispersity. Followed by cationic molecules were covalently linked to the desulfated CNCs to invert the surface charge. Lastly, the synthesized cationic CNCs and purified anionic polymeric siRNAs were incorporated into nanocomplexes (PsCNCs) via electrostatic interaction. The results indicated that the nanocomplexes revealed significantly improved enzymatic stability against RNase degradation, RNAi-mediated regulation of the target gene with negligible cytotoxicity, and inhibition of apoptosis-induced proliferation of cancer cells [80].

Burt et al. employed NCC as a carrier of anticancer drugs (DOC, PCT and Etoposide). Then Burt et al. modified the surface of NCC by binding a cationic surfactant, CTAB, ensuing in a concentration-dependent rise in the zeta potential of NCC. Hence, their

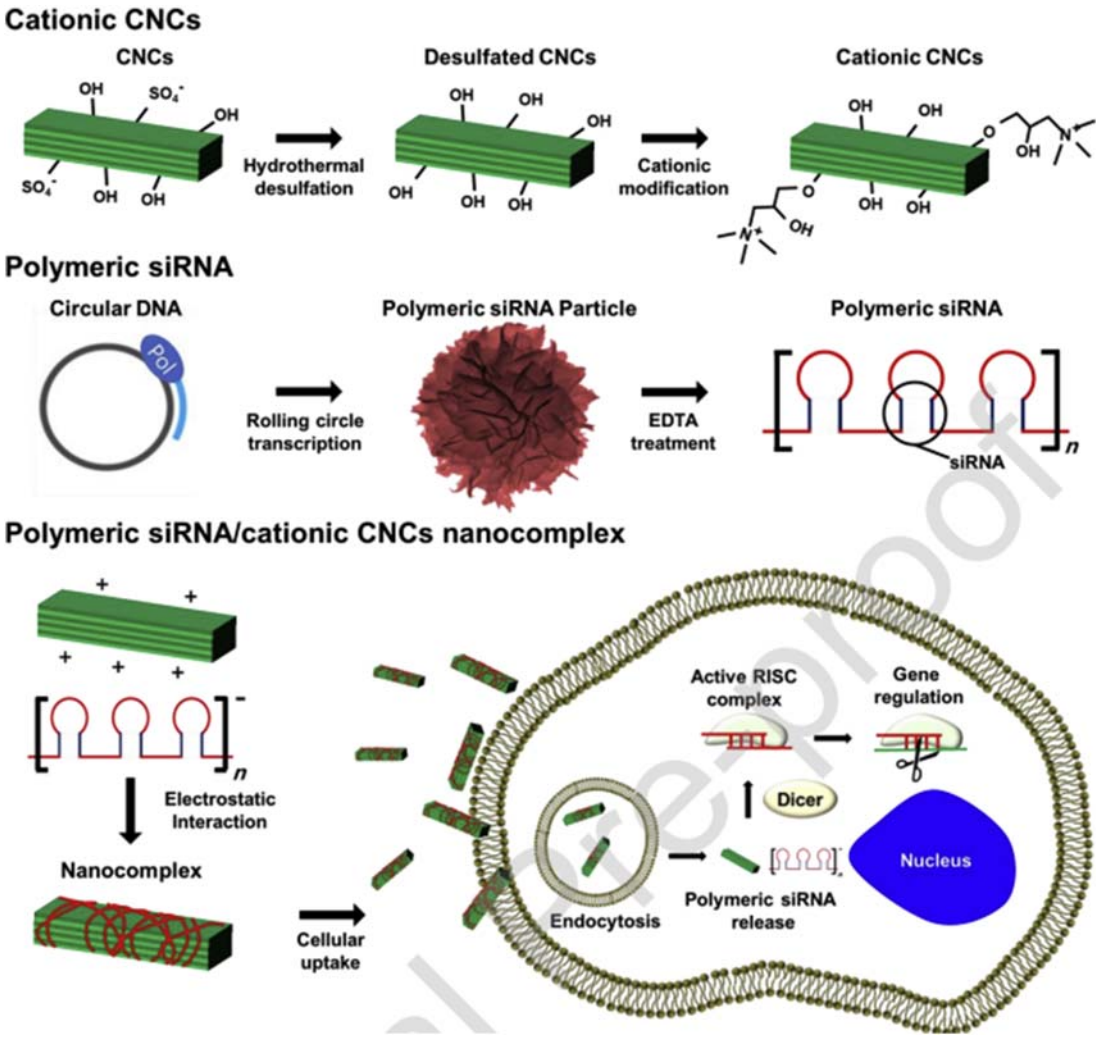

Figure 5.12

Schematic diagram showing synthesis process of generation of PsCNCs for polymeric siRNA delivery to cancer cells. *From Copyright 2020, Elsevier Y.M. Kim, Y.S. Lee, T. Kim, K. Yang, K. Nam, D. Choe, Y.H. Roh, Cationic cellulose nanocrystals complexed with polymeric sirna for efficient anticancer drug delivery, Carbohyd. Polym. (2020). https://doi.org/10.1016/j.carbpol.2020.116684.*

findings indicated a controlled drug release in several days [81]. Furthermore, Mohanta et al. developed thin films as drug carriers using NCC along with chitosan, a cationic complementary polymer. In fact, the amine groups of chitosan can interact with the sulfonate groups of NCC electrostatically. They observed that loaded both water-soluble and water insoluble anticancer drugs into films, DOX HCl and CUR, respectively. They observed that the most important interactions of DOX and CUR with NCC were hydrogen

bonding reactions (OH···O and CH···O) with van der Waals interactions. Based on their study, DOX release in acidic conditions (pH 6.4) was higher due to the protonation of the amine group that helped the diffusion process leading to a superior solubility. Amusingly, this could be more preferable for cancer treatment as the extracellular pH of tumor cells is acidic (∼6.5−6.9) [82]. Kolakovic et al. discovered the application of NFC as a matrix former material for sustained delivery of indomethacin, itraconazole, and beclomethasone as transdermal patches. They developed film-like matrix systems with drug loadings between 20% and 40% via the filtration technique. As per the to their findings, drug released in a sustained manner up to 3 months, proving NFC as an attractive material for controlled release of poorly water-soluble drugs [83]. Cellante et al. studied CNC functionalized with chlorotoxin-o-peptide by using a simple and mild one step fisher esterification. Cell viability studies confirm that both CNCs and functionalized CNCs have no contact on cell viability. Furthermore internalization studies with fluorescence microscopy discovered that cellular uptake of nanocrystals can be modulated in relation to their linkage with chlorotoxin: Especially chlorotoxin increases the hold of CNCs for U87MG cells in function of their prominent term of MMP2, a typical feature of GBM cells [84].

2.4.6 Nanogel

Nanogels are the 3D-bionanoparticles produced by chemically or physically cross linked polymers with hydrophilic or amphiphilic macromolecular chains, capable to swell by hold a great amount of water, without dissolving by maintain the structure intact [85,86]. The huge amount of water content correlates with the fluid-like transport properties for the biologically active molecules considerably smaller than the gel pore size. Nanogels can be serene of a variety of natural polymers, synthetic polymers or a combination thereof, chemically (covalent) cross linked or physically cross linked with non-covalent bonds by hydrogen bonds or electrostatic or hydrophobic interactions. The immense capacity of absorbing water is accredited to the presence of hydrophilic functional groups, such as −OH, −CONH−, $-CONH_2-$ and $-SO_3H$, along the macromolecular chains in the polymer structure [85]. Oh et al. carried out the grafting of diethylaminopropyl groups to glycol chitosan nanoparticles to encourage the pH sensitivity with the aim of releasing DOX from the cross linked nanogel [87]. Jaiswal et al. reported in their study that for biomedical applications wherein the therapeutic agents are delivered under specific physiological conditions, forever more than one stimulus sensitive nanogel system is necessary. They synthesized a dual stimuli pH and temperature-responsive nanogel based on poly (N-isopropyl acrylamide)-chitosan for hauling and delivering an anti-cancer drug − doxorubicin at specific sites, triggered by one of the stimuli. Chitosan a natural biopolymer with pendant amino groups may be an alternative as it protonates and solubilizes in weak acidic medium. In additional by grafting of chitosan to poly (N-isopropyl acrylamide) segments, a shifting to higher temperature of LCST is obtained.

Hence, a nanogel based on poly (N-isopropyl acrylamide)-chitosan be capable of form a dual pH and temperature stimuli-sensitive network [88]. Li et al. identified the potential use of ethylenediamine (ED)-functionalized low-molecular-weight PGMA nanogels (PGED-NGs) as effective siRNA and pDNA carrier. To enhance pDNA and siRNA transfection, a natural antioxidant, lipoic acid (LA) was introduced into ED functionalized PGMA and cross linked to produce cationic reducible PGED-NGs with plentiful disulfide linkages. These nanogels cross linked with disulfide linkages compared with unmodified PGED exhibited better performance of pDNA transfection and target-specific intracellular delivery of MALAT1 siRNA into hepatoma cells suppressing cancerous cell proliferation and migration [89]. Yang et al. investigated the encapsulation of vascular endothelial growth factor (bFGF) and pDNA encoding VEGF165 genes within heparin-conjugated supra molecular pluronic nanogels pre-coated with PEI to study cells differentiation and proliferation. HPebFGF/PEI nanogels encapsulated with bFGF and VEGF165 pDNA gene complex were uptake by human endothelial progenitor cells (EPCs) most likely due to the conjugated heparin that facilitated cell membrane penetration. Thus HPebFGF/PEI nanogels had then the ability to competently promote endothelial cell differentiation and regeneration of vessels in the tissues of an ischemic limb model system [90]. Nano gel-based systems target the transcellular routes of drug transport in brain micro vessel endothelial cells. Therefore exploration of the specific peptides for targeting the drug as well as receptor-mediated transcytosis across the BBB is impending strategies for improving drug delivery to the brain. Nanogels can be modified to develop therapeutic cargos that are capable to traverse the BBB (Fig. 5.13). Such modification is via receptor or ligand binding, in addition to opportunity of adding magnetic features to the nanostructure, which could allow these carriers to traverse other dynamic barriers in the body. Furthermore, hydrophobic modifications of their surface render them more capable to cross the BBB. Their outstanding ability to respond to external stimuli could also be utilized for the delivery of cargos using external stimulation, such as ultrasound and magnetic fields [85].

2.4.7 Emulsion based drug delivery systems

Emulsions are thermodynamically unstable colloidal dispersions that are generally prepared from two fluids that are immiscible with each other (typically oil and water in foods), with lone of the fluids being dispersed as small spherical droplets in the new one. The emulsion based drug delivery systems, which composed of small oil droplets dispersed in water, as these are the type of emulsion most normally used as a colloidal delivery system within the food industry. The precise size of the oil emulsion depends on the type and concentration of emulsifier and oil used, as well as on the homogenization method engaged. Based on particle size they are classified as Nanoemusions, Microemulsion, submicron emulsions, SNEDDS, SMEDDS and etc [91]. Izgelov et al. investigated the effect of the lipid component in self-emulsifying DDS on the oral

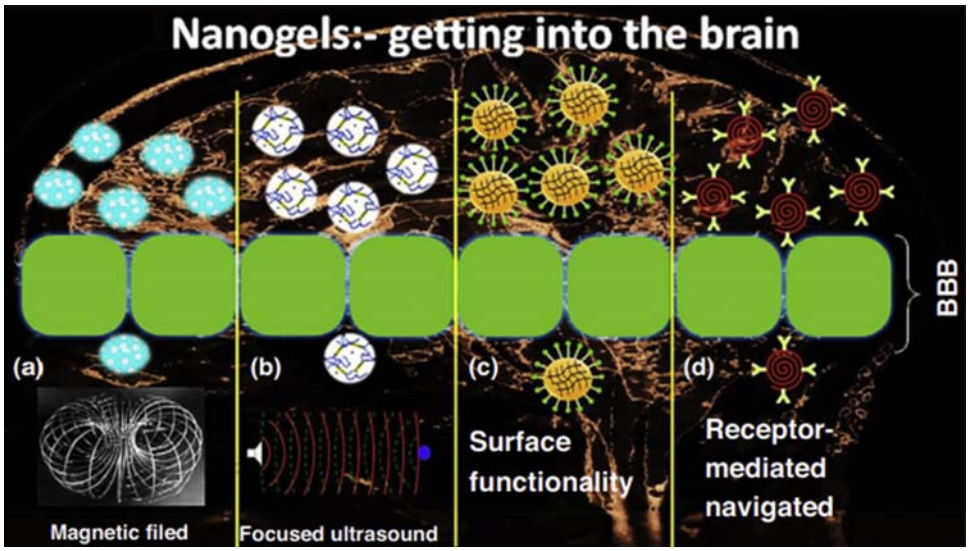

Figure 5.13

Schematic presentation of the various suggested mechanisms by which nanogel-based drug delivery systems might cross the blood–brain barrier (BBB). Nanogel-based nanoformulations can be: (A) magnetic, to allow magnetically guided non-invasive delivery; (B) delivered to the brain via opening the BBB using external stimulation, such as focused ultrasound; (C) hydrophobic to achieve delivery to the brain; and (D) carry receptor-functionalized cargo that is able to cross the BBB. *From Copyright 2018, Elsevier A.Q. Vashist, A. Kaushik, A. Vashist, J. Bala, R. Nikkhah-Moshaie, V. Sagar, M. Nair, Nanogels as potential drug nanocarriers for CNS drug delivery, Drug Discov. Today 23 (7) (2018) 1436–1443.*

absorption of most important cannabinoids Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) using either long chain triglycerides (LCT) or medium chain triglycerides (MCT) with diverse ratios. The developed formulations were thermodynamically stable oil-in-water with particle size of 50 nm. Izgelov et al. demonstrated that the effect of each type of lipid on bioavailability of cannabinoids is not straightforwardly anticipated in rat model. The difference in the result of LCT and MCT on absorption was not substantial for MCT formulations, though, more prominent LCT formulations [92]. Batool et al. was investigated by manufacturing TMX loaded SNEDDS using papain grafted S-protected hyaluronic acid-lithocholic acid co-block (PAP-HA-ss-LCA) polymeric excipient for targeting breast cancer epithelial cells over expressed with CD44 receptors. *In vitro* cytotoxicity studies confirmed that TMX-PAP-HA-ss-LCA SNEDDS could proficiently kill MCF-7 breast cancer cells as compared to the native TMX drug. Systemic toxicity studies proved the non-toxic nature of TMX-PAP-HA-ssLCA in contrast to pure TMX. So, they have, confirmed TMX-PAP-HA-ss-LCA SNEDDS formulation seem to be capable mucopermeating, increased intracellular uptake with strong targeting possible for antiproliferative activity [93]. Fopase et al. synthesized a

nanoemulsion based DDS using the combinations eucalyptus essential oil and surfactant by encapsulating DOX for the improving antibacterial and anticancer features. The developed emulsion found to be spherical, with an average size of 175 ± 18 nm and displayed an enhanced broad-spectrum antibacterial activity with the comparable IC_{90} value to the Kanamycin. The DOX loaded emulsion was shown to be highly efficient against cancer cells and its inhibitory concentration (IC_{50}) value was decreased by 10 folds as compared to only DOX [94]. Schultze et al. evaluated the cytotoxic effect of CUR-loaded lipid-core nanocapsules over short and extended periods of time on MCF7 compared to CUR-loaded nanoemulsion and CUR DMSO-water solution. The group treated with nanoemulsion exhibited the lowest inhibition rates at 24 h. Differences between groups, except for non-encapsulated CUR, moved out at 48 h. At 72 h, the highest inhibition rates were an experiential in the group treated with non-encapsulated CUR. Conversely, CUR-loaded lipidcore (formulation with caprylic/capric triglycerides mixture in core) exhibited important difference from the other groups: $F(3, 16) = 21.01$, $P < .001$ at 24h, $F(3, 16) = 6.287$, $P < .01$ at 48 h and $F(3, 14) = 9.098$, $P < .01$ at 72 h [95].

2.4.8 Polymer conjugates

Polymer–drug conjugate therapeutics are pharmacologically active macromolecular structures consisting one or more therapeutic agents together with small molecules, peptides, proteins and aptamers covalently bound to a polymeric carrier. The conjugation of bioactives to polymers confers several benefits, includes improved drug solubilization, controlled delivery, improved efficacy and enhanced pharmacokinetics. Though, the first polymer–drug conjugate was reported in 1955 by Jatzkewitz, the field of polymer therapeutics was propelled by the seminal work of Ringsdorf, Kopecek and Duncan and others, in the 1970 [96,97]. The substantial clinical usefulness of polymer conjugation was comprehend in 1990 with the first market consent of a polymer–protein conjugate, Adagen, an enzyme replacement therapy for adenosine deaminase deficiency in patients with severe combined immunodeficiency [98,99]. The first marketed PEG–protein therapeutic, Adagen, established clinical approval in 1990. Adagen is a PEG–adenosine deaminase conjugate used for the treatment of severe combined immunodeficiency caused by an innate deficiency of the adenosine deaminase enzyme [100]. Huang et al. was developed a nano polymer conjugate based on disulfide cross-linked low-generation peptide dendrimers for collective treatment of colon cancer and its thrombotic complications, as depicted in Fig. 5.14. Initially, two-generation polyglutamic acid dendrimer (G2) was synthesized and bonded nattokinase (NK) to obtain NK-G2 by amidation between carboxyl groups on G2 and amino groups on NK. Then, cystamine containing disulfide linkages was used as a cross-linker to make polymer conjugates (NK-G2)n, and then encapsulated DOX to form DOX -(NK-G2)n. While internalized by cancer cells, the conjugates would disconnect and release DOX to kill cancer cells after

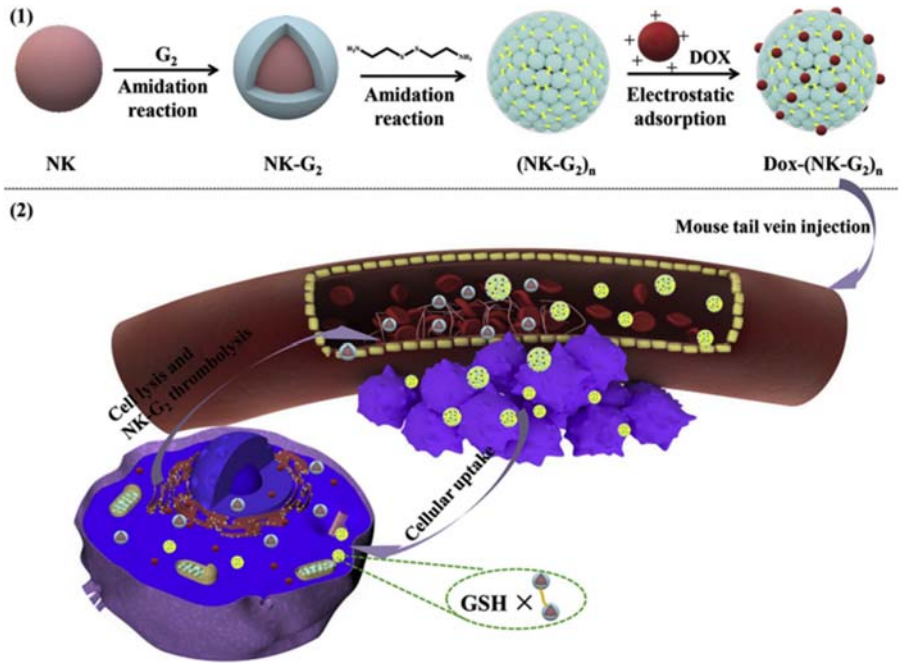

Figure 5.14

Schematic illustration for (1) the formation of drug loaded polymer conjugates based on low-generation peptide dendrimers cross linked by disulfide linkages, and (2) the mechanism of combined therapy for colon cancer and thrombotic complications. *From Copyright 2020, Elsevier M. Huang, Y. Ji, J. Yan, T. Qi, S.F. Zhang, T. Li, S. Lü, Y. Liu, M. Liu, A nano polymer conjugate for dual drugs sequential release and combined treatment of colon cancer and thrombotic complications, Mat. Sci. Eng. C 110 (2020) 110697.*

disulfide linkages were broken at high concentration of glutathione (GSH, ~10 mM), regarding 10 times higher than blood circulation and tumor extracellular environment. Subsequently, NK would diffuse and treat thrombotic complications, hence achieving the goal of releasing drugs successively and combined treatment of colon cancer and thrombosis [100].

Randarova et al. reported on novel synthesis and in vivo evaluation of well-defined biocompatible hydrophilic copolymers based on N-(2-hydroxypropyl) methacrylamide (HPMA) and their drug conjugates with pirarubicin enabling controlled drug delivery and pH-triggered drug activation in tumor tissue. The developed polymer drug conjugates revealed improved biological behavior in vivo, particularly the prolonged blood circulation, urine elimination, tumor accumulation and excellent anticancer activity. They reported that the prepared well-defined polymer conjugates could considerably enhance tumor therapy in humans [101]. Another study stated that antibody-conjugated targeted delivery system self-possessed of polymer-dendron conjugates. Trastuzumab is selected as

the targeting moiety, as it is clinically used against tumor cells expressing HER2 receptors. A micellar delivery system was generated with amphiphilic polymer-dendron conjugates contain fourth generation polyester dendron as the hydrophobic block and linear PEG chain as the hydrophilic block. Subsequent to incorporation of DOC (ca. 10% wt) into micelles; trastuzumab was conjugated onto the micellar shell using amidation reaction. DOC release was indomitable to be responsive to acidic pH, and over the course of 30 h, 54% drug release was considered in acidic media, while it was around 30% in neutral conditions. Cytotoxicity experiments on MCF7 and SK-OV-3 cell lines displayed enhanced toxicity levels for targeted micelles in contrast to the non-targeted counterparts, while pulse-chase experiments indicated efficiency of micellar formulations, in addition to presence of targeting groups. Cellular internalization study additional confirmed the enhanced cellular uptake of antibody conjugated targeted micelles [102].

2.5 Lipid bionanomaterials

2.5.1 Lipoprotein

Lipoproteins are bionanoparticles that transport cholesterol and other lipids in the blood; their size ranges starting 8−1200 nm. Since they are endogenous carriers, lipoproteins are not accepted as foreign entities by the human immune system and are not absorbed by the RES. Whereas, result lipoprotein nano platforms may afford a solution to the biocompatibility issues associated with most synthetic nanostructures [103]. Low Density Lipoprotein is naturally happening bionanoparticles that has long been used as vehicles for the specific delivery therapeutic agents of and diagnostic to tumor cells [104]. LDLBNPs are renowned by and internalized in cells through specific membrane receptors that a combine with the apoprotein B-100 (apoB-100) [105]. The entrance of nanoparticles into cells is mediated by numerous mechanisms, including clathrin-mediated transport, caveolae-dependent endocytosis and macropinocytotic uptake. Additional mechanisms like electrostatic forces, van Der Waals or steric interactions are concerned in the entry of nanoparticles into cells [106]. The receptor-ligand complex pathway may be useful for drug delivery, and may afterward be directed toward tumors expressing LDLR. Some drugs incorporated into the LDL particle accumulate within the targeted cell; provide a very effective mechanism for drug delivery [107]. Accordingly, LDL-based hydrophobic/amphiphilic DDS can be internalized and degraded by regular cell metabolism, and these properties can be used in targeted therapies for cancer [108]. Fig. 5.15 expressed cellular uptake of LDL loaded with drug [107].

LDL could be employed as carriers to conjugate water-insoluble anti-cancer drugs to lead to a superior accumulation of the drugs at specific locations. This property might permit the particle to deliver its loaded drugs and avoid drug degradation. LDL has a high attraction for and may accumulate in tumor cells. LDL has as well been used as a carrier

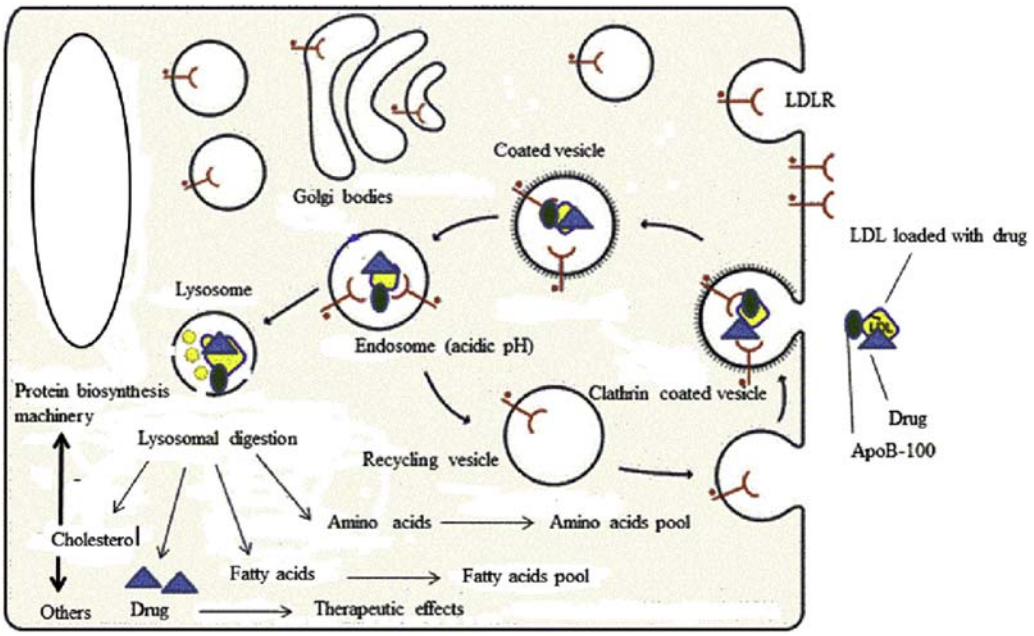

Figure 5.15

Steps of cellular uptake and recycling of LDL loaded with drug by LDLRs. Plasma LDL can be cleared from circulation through LDL receptor (LDLR)-mediated endocytosis. This allows for the transfer of LDL into endosomes, where the pH drops, causing LDL to dissociate from the receptor. The receptor is then recycled to the surface of the cell, while LDL is transferred into the lysosomes for degradation. This pathway could be useful for drug delivery, and may then be directed toward tumor cell over expressing LDLRs. *From Copyright 2014, Elsevier G. Harisa, F.K. Alanazi, Low density lipoprotein bionanoparticles: from cholesterol transport to delivery of anti-cancer drugs, Saudi Pharmaceut. J. 22 (6) (2014) 504–515.*

to deliver anti-tumor drugs into hepatoma cells to treat hepatocellular carcinoma [108]. Masquelier et al. discovered the prospect of using LDL as a drug carrier to increase the selectivity of anti-tumor drugs in cancer chemotherapy and initiate that the sequestering of anti-tumor agents with LDL does not affect the drugs characteristics [109]. Chu et al. have been developed DOX attached human LDL to form an LDL-DOX complex. When the complex was injected into mice, more LDL-DOX accumulated in the liver than free DOX. In distinguish, less LDL-DOX accumulated in the heart than free DOX [110]. Nikanjam et al. have been developed synthetic lipoprotein coined ‘‘nano-LDL’’ targets cancer cells, especially glioblastoma multiforme, is calm of a peptide fragment anchored to the particle via a lipid and binds the LDLRs [111]. The nano-LDL particle was capable to include the PCT prodrug at 0.33 mg/mL; the ensuing nanoparticle was highly toxic to multiple glioblastoma multiforme cell lines expressing variable amounts of the LDLRs. Most neurons do not express high levels of the LDLRs, which may make this vehicle highly

selective for glioblastoma multiforme cells in the brain [111]. PDT is currently standard for the treatment of esophageal, bladder and lung tumors for both therapeutic and calming purposes. Numerous lines of confirmation indicate that the selectivity and efficiency of tumor targeting by porphyrins and their analogs are improved by increasing the hydrophobicity of the molecule [104]. Polo et al. have been developed suitable formulations of PDT agents in liposomal vesicles or LDL particles to permit for the systemic administration of poorly water-soluble porphyrin derivatives. Pharmacokinetic studies with tumor-bearing mice confirmed that various liposome-associated porphyrinoids are proficiently transferred to serum lipoproteins, particularly to LDL, upon intravenous injection and therefore lead to a high tumor uptake [104]. The targeted delivery of drugs in complex with LDL into tumor cells is promising owing to the improved expression of specific LDLRs in various types of transformed cancer cells compared to non-transformed cells [112].

2.5.2 Nanosuspensions

NS are suspensions form of drug nanoparticles with size ranging from 10 to hundreds of nanometers [113]. Absence of carrier chemicals endows NS with high drug loading of 50%−100% (w/w), being significantly superior to that of conventional nanoparticles. In addition, the improved specific surface area owing to size reduction significantly increases the dissolution of water insoluble drugs, leading to the initial application of NS in oral delivery for improved bioavailability. Recently, NS found various applications in drug delivery. The booming marketing of rutin NS (Juvedical) in cosmetic product promote encourages research and development in this field [114]. Oktay et al. developed an FB based gel and evaluated its analgesic and anti-inflammatory activities in rats. FB-NS was prepared by the wet milling method with Plantacare 2000®, as stabilizer. The FB-NS was followed by incorporated in diverse carrier gels such as HPMC, polycarbophil, oleogel, and chitosan. Then analgesic and anti-inflammatory activities of the optimum NS based gel were evaluated using the tail flick and carrageenan-induced paw edema methods consecutively. The NS was successfully prepared with the wet milling method, and the PS, PDI and ZP values were found to be 237.7 ± 6.8 nm, 0.133 ± 0.030, and -30.4 ± 0.7 mV; respectively. The anti-inflammatory activity of FB-NS HPMC gel was higher than that of the physical mixture gel and that of the coarse suspension gel. Furthermore, analgesic activity studies exhibited that, in the 180th min of FB NS treatment, the latency time was significantly prolonged compared to that of the control group. Whereas NS increased the in vivo pharmacodynamics effect of FB by means of nanosized particles and a large surface area [115]. Alshweiat et al. was prepared by antisolvent precipitation method followed by ultrasonication and were evaluated for in vitro dissolution and diffusion, in addition to in vivo studies in a rat model. Loratadine NS had shown a particle size of 311 nm, a PDI of 0.16, and ZP of −22.05 mV. Furthermore, using a mucoadhesive agent is crucial to extend the contact time between the formulation and nasal mucosa. Moreover,

NS showed enhanced dissolution in an artificial nasal fluid. As well, higher diffusion and permeability coefficient compared to the unprocessed loratadine. The confirmation from the in vivo studies showed the superiority of nasal delivery over the oral administration [116].

Mohammad et al. developed nanocrystals by encapsulating co-delivery of DSF and PCT for treatment of MDR by using a DDD strategy (Fig. 5.16). Nanocrystals exhibited the 160-nm PTX-DSF Ns with rod-like morphology had drug-loading up to 43% at mass ratio of 5:1. Fascinatingly the nanoparticles entered cells via caveolar endocytosis. By reducing intracellular ATP level and GST activity, PTX-DSF Ns killed the Taxol resistant A549 cells with higher efficiency than PTX alone, exhibit as 6-fold increase of apoptosis in MDR tumor. The nanoparticles dispersed in blood over time, accumulate in tumor professionally and reduced the tumor volume by 12-fold in MDR tumor-bearing BALB/c nude mice and permissible 12-fold apoptosis in tumor. Furthermore, the

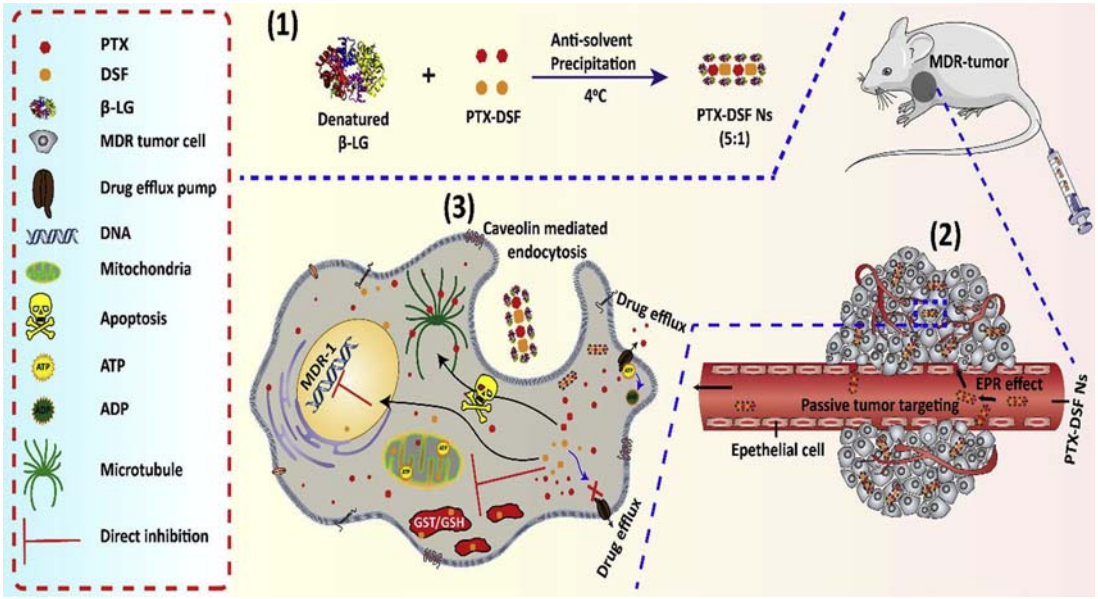

Figure 5.16

PTX-DSF Ns (5:1) were prepared by antisolvent-precipitation method and injected into MDR-tumor bearing mice, (2) accumulated at the tumor site, and (3) were taken up by tumor cells by caveolin-mediated endocytosis where they deliver a synergistic concentration of PTX and DSF. The released DSF suppressed over expressed MDR-1 associated P-gp efflux pump, decreased intracellular ATP production and decreased GST enzyme activity, therefore increased intracellular PTX concentration and induced enhanced apoptosis of MDR tumor cells. *From Copyright 2019, Elsevier I.M. Mohammad, C. Teng, B. Chaurasiya, L. Yin, C. Wu, W. He, Drug-delivering-drug approach-based codelivery of PCT and disulfiram for treating multidrug-resistant cancer, Int. J. Pharm. 557 (2019) 304–313.*

immunohistochemical examination confirmed the safety of the nanoparticles. In general, the DDD strategy-based PTX-DSF Ns have capable potential for the treatment of MDR cancer [113].

2.5.3 Liposomes

Liposomes are part of nanoparticles that are able of introducing both lipid-soluble and water-soluble drugs. This entrapment protects the drug from quick degradation and reduces drug toxicity by building it occupied to the systemic circulation. Liposomes can also progress the therapeutic index of a new or recognized drug by changing the drug's pharmacokinetic properties such as absorption and metabolism, rising its biological half-life, or dropping its elimination. It has a hydrophilic outside/inside and a hydrophobic layer that can allow it to incorporate a variety of drugs and assist delivery to the preferred site. To exploit this specialized vehicle, several anticancer drugs (including marketed) have been formulated to have special targeted delivery options [117]. Presently, liposomes have develop into one of the most trendy delivery vehicles as an experimental model and commercially as a drug delivery system because they have low toxicity, biodegradability, biocompatibility, entrapment capacity of both hydrophilic and lipophilic drugs, and alleviate of target-specific drug delivery to malignant tissues. Targeting particular cells and reduction of drug toxicity in the liposomal formulation has confident researchers to carry out various studies focusing on liposome-based drug delivery [118]. The solubility of poorly water-soluble antitumor drugs can be improved throughout liposomes to advance existing cancer treatment regimens. Moreover, long-circulating liposomes can reduce the uptake by MPS, which eventually increase a passive accumulation into the tumor area. Attaching targeted ligands (e.g., peptides) to the liposomal surface can also help to get active-tumoral targeting [119]. The size of the liposomes has an effect on passive accretion and effectual retention on the targeted site of action (Fig. 5.17). These methods diminish drug deterioration and metabolic inactivation of a drug after treatment. As well, the amount of drug delivered and drug's bioavailability within the exaggerated area increases, thus humanizing efficacy and/or reducing drug toxicity [120].

The EGFR receptor family (EGFR, HER-2, and HER-3) erstwhile found to be over expressed in a variety of forms of cancers such as non-small cell lung cancer [121] and breast cancer [122]. Two separate liposomal formulations were developed to entrap doxorubicin and vincristine characteristically with surface modification by αHER-2 Fab' fragments with targeted Asn-Gly-Arg peptides to deliver the drug selectively into endothelial cells in tumor vasculature and tumor cells against HER2-positive breast cancer [123]. Dai et al. prepared liposome containing an integrin α5β1 antagonist N-acetyl-proline-histidine-serine-cysteine-asparagine-amide (AcPHSCN-NH2) as a novel targeting peptide, which is in clinical trials for cancer therapy. This formulation (PHSCNK-PL-DOX) and contains DOX as a chemotherapeutic agent. PHSCNK-PL-DOX

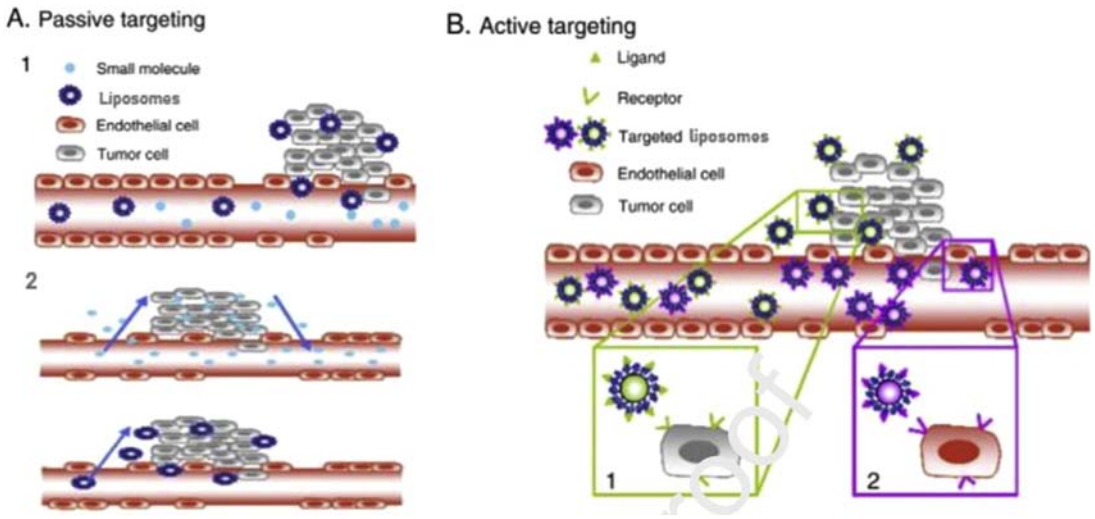

Figure 5.17

A. Passive targeting of liposomes. (1) Selective accumulation of liposomes through leaky vasculature surrounding the tumors. (2) Size-dependent retention of liposomes in the tumor tissue. Drugs alone can diffuse back to the bloodstream, reducing drug concentration in the targeted site, while drug-loaded liposomes stay concentrated in the targeted site due to its particle size. B. Active targeting strategies. Targeting peptides grafted at the surface of liposomes bind to receptors (over)expressed by (1) cancer cells or (2) angiogenic endothelial cells. *From Copyright 2020, Elsevier M.A. Tran, R.J. Watts, G.P. Robertson, Use of liposomes as drug delivery vehicles for treatment of melanoma, Pigment Cell Melanoma Res. 22 (2009) 388–399.*

showed enhanced intracellular incorporation as well as superior cytotoxicity against melanoma B16F10 cells compared to control DOX-only liposome PL-DOX. This targeted formulation revealed capable results in terms of better tumor inhibition and increased survival time compared to a control in an in vivo study, at the alike time indicating lowered cardiovascular toxicity in tissue analysis. The pharmacokinetics and biodistribution results demonstrated that the integrin $\alpha 5\beta 1$ antagonist-incorporated liposomal formulation can be used as a potential therapeutic agent for targeted cancer therapy [124]. Jiang L et al., investigated whether novel liposome formulations loaded with TGF-β1 could endorse the odontogenic differentiation of human dental pulp stem cells (hDPSCs) for dentine-pulp regeneration. The drug release results revealed that liposomal TGF-β1 achieved a controlled and prolonged release over time. The MTT results confirmed that the liposomes (100 μg/mL) were not cytotoxic to the cells. Liposomal TGF-β1 up-regulated the appearance of "osteodentine" markers, RUNX-2, DMP-1 and DSPP, in hDPSCs after 7 days of treatment and resulted in the accretion of mineralized nodules. Finally they indicated that liposomes are an effective carrier for

delivering TGF-β1 over time. Liposomal TGF-β1 promoted dentinogenesis and increased mineralization in hDPSCs. This places of interest the potential of liposomal TGF-β1 for future use in dentine-pulp renaissance [125].

2.5.4 Lipopolyplexes/polyplexes

Gene therapy is a capable approach to treat genetics deficiencies and various acquired diseases [126]. This novel therapeutic advance will be fully equipped when smart systems will be capable to efficiently initiate foreign genes into the target cells and let high gene expression levels. Though viral vectors are presently the most resourceful systems, safer methods need yet to be developed [127,128]. The employ of cationic lipids and cationic polymers for gene transfer was introduced by Felgner et al. (1987) and Wu and Wu (1987), respectively [129]. Their use has encouraged quickly from transfection of cell cultures to clinical gene therapy applications. Amongst about 60 synthetic transfection agents that are accessible commercially, more than half are based on the use of cationic reagents. Cationic lipid/DNA complexes (lipoplexes) and cationic polymer/DNA complexes (polyplexes) employed in gene therapy are based on the hypothesis that the complexes adsorb further efficiently to the anionic plasma membrane of mammalian cells via electrostatic interactions. Compare with other non-viral delivery systems, as well as anionic liposomes that encapsulate nucleic acids, lipoplexes and polyplexes be inclined to mediate a higher level of transfection in numerous cell lines. To facilitate the use of lipoplexes and polyplexes in gene therapy and to progress their transfection efficiency, their mechanism of action is being investigated in many laboratories [130]. Nanoparticles such as liposomes, polymeric micelles, lipoplexes, and polyplexes are often investigated as the drug carrier systems for delivery of these valuable molecules. Since the electrostatic complexation of the positively charged polymers with the negatively charged siRNA molecules is the most common strategy for gene delivery, employing these polymers are more favorable [131]. For example Chow MYT et al., summarized the critical steps for the development of successful pulmonary RNA delivery system (Fig. 5.18), and discussed. Generally, it is pleasing to use delivery vectors that reveal cell-targeting properties with the capability to conquer the specific barriers associated with the disease concerned. A systematic understanding of the excretion pathway is required to make sure that the delivery vectors would not accumulate in the body, particularly when synthetic or nonbiodegradable materials are used. Vectors with soaring loading ability could evade the use of excessive excipients, thereby minimizing the risk of toxicity. Additionally, to evaluate the in vivo efficacy of the delivery system, RNA is frequently administered intratracheally to the lung of animals either as large droplets instilled by pipette or as a fine spray aerosolized by a microsprayer or similar device. Evidently, these administration methods are unreasonable for human use. For clinical practice, RNA drugs can be delivered whichever as liquid aerosols during nebulization or as dry powder for inhalation (Fig. 5.18). As the previous can deliver high doses of liquid formulations over a period of

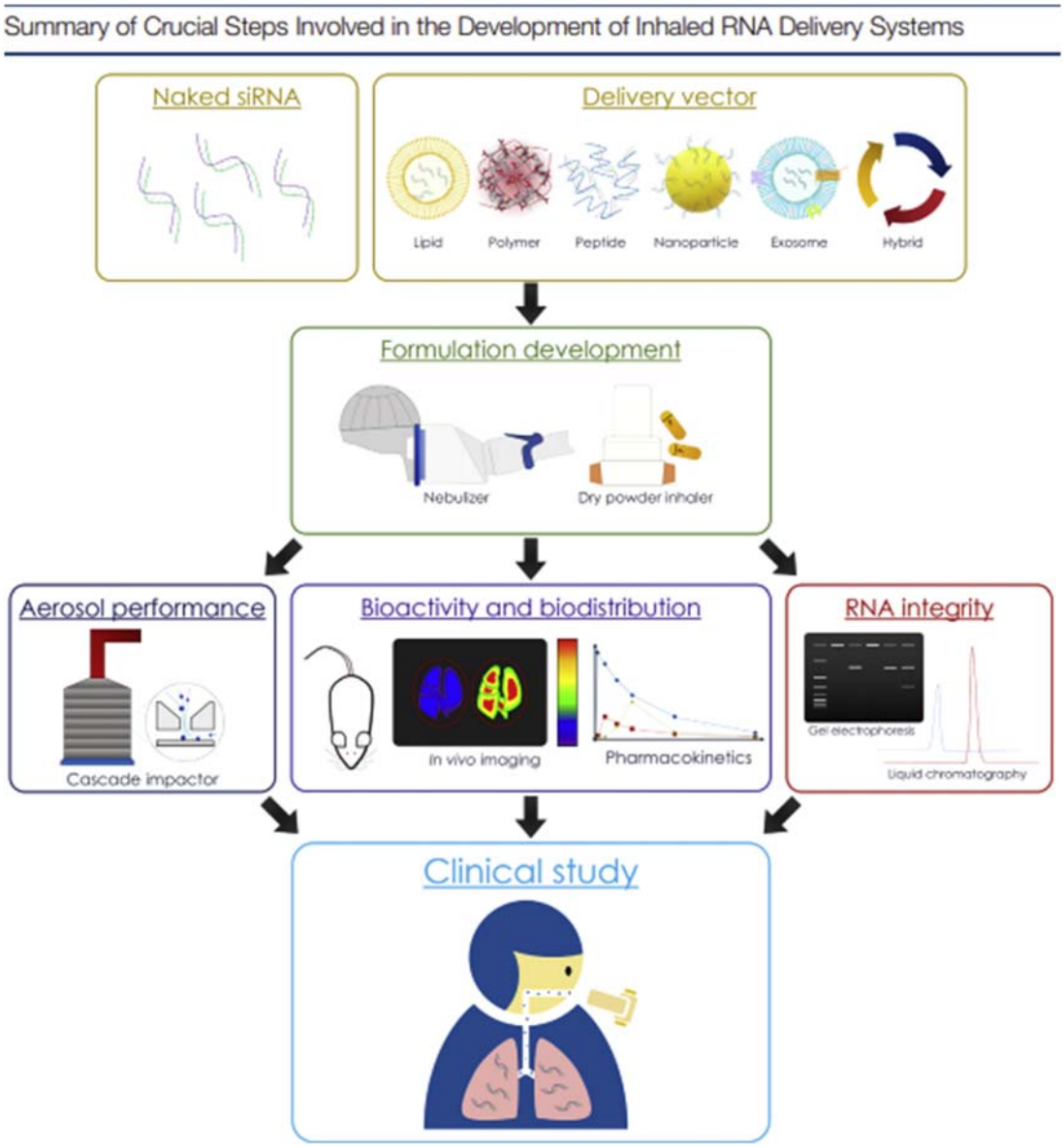

Figure 5.18

Firstly, either naked RNA is used or a delivery vector is designed to facilitate the uptake of RNA therapeutics to the targeted cells. A formulation (liquid or powder aerosol) is then developed with the identification of a suitable inhalation device for clinical use. The formulation is thoroughly characterized and evaluated for its aerosol performance, RNA integrity after aerosolization, and the biological activity and pharmacokinetic profile of the inhaled formulation in suitable animal models. Lastly, the potential candidates are identified for clinical study. *From Copyright 2020, Elsevier M.Y.T. Chow, Y. Qiu, J.K.W. Lam, Inhaled RNA therapy: from promise to reality, Trend Pharmacol. Sci. 41 (10) (2020) 715–729.*

time (typically ∼10−20 min, depending on the dose), the second is more portable and convenient to use. Though, there are rigorous requirements for particles to be suitable for inhalation in clinical settings and animal studies cannot reflect the "inhalability' of a formulation. Amazingly, only an only some studies have evaluated the aerosol performance of RNA formulations designed for inhalation. A good perceptive of the aerosol properties of the formulation could improve the chance of successful clinical translation (Fig. 5.18). Furthermore nebulizers or dry powder inhalers are desired to generate aerosol for inhalation. Specified that both devices could damage the fragile RNA molecules (especially single-stranded mRNA) owing to the high shear stress during aerosolization, it is essential to examine the RNA integrity, in provisos of physical structure and biological activity, in the aerosolized particles (Fig. 5.18). Another area that require concentration during development of a pulmonary RNA delivery system is indulgent the biodistribution and pharmacokinetic profile of the inhaled RNA formulation (Fig. 5.18) [132].

Ming X et al., examined internalization mechanisms of antisense oligonucleotides formulated into cationic lipoplexes and polyplexes with pharmacological and genetic inhibitors of endocytosis. The mechanistic study exposed that the SSOs delivered by lipoplexes enter the cells largely by membrane fusion and this mechanism as well accounts for the functional induction of the target gene, whereas PEI/SSO polyplexes are internalized by unconventional endocytosis pathways that do not need dynamin and caveolin functions. Finally they propped that these mechanisms may help rationally design novel delivery systems and also help comprehend the toxicity related with these delivery systems [133]. When vascular endothelial growth factor in choroidal neovascularization is a major reason of visual loss of the elderlies and diabetics, gene therapy may recommend an alternative treatment. Though, siRNA instability and ineffective delivery are the main hindrances. To address this issue, Chaharband et al. developed a nano-sized siRNA loaded therapeutic delivery system using chitosan-hyaluronic acid nano-polyplexes. The developed nano-polyplex resulted with a narrow size distribution indicated no significant cytotoxicity. The intravitreally given nano-polyplexes in rabbits overcame both the vitreous and retina barriers and reached the posterior tissues proficiently. Intravitreal injections of the VEGFR-2 siRNA nano-polyplexes significantly abridged the size of the laser-induced choroidal neovascularization, compared to the control group. Therefore, the developed formulation can be a capable candidate for intravitreal delivery of siRNA [134].

2.5.5 Solid lipid nanoparticles

SLNs are at the portent of the rapidly developing area of nanotechnology with a number of potential applications in drug delivery and research. SLNs are physically stable to protecting the included labile drugs from degradation, controlled release, limits coupled

problems low wonderful suitability at the same instance, cost-effective [135]. SLNs formulations for assorted application routes have been developed such as parenteral, oral, dermal, ocular, pulmonary, and rectal and systematically also characterized in in-vitro and *in-vivo* studies [136]. SLNs made up of solid lipid (lipids solid at room temperature at human body temperature), stabilized with a surfactant (emulsifier), co-surfactant (water/solvent) and active in gradients [137]. The lipids used might be triglycerides (tri-stearin), partial glycerides (Imwitor), fatty acids (stearic acid, palmitic acid), steroids (cholesterol) and waxes (cetyl palmitate). They have comparatively higher drug entrapment proficiency, render the drug progressively stable in their lipid matrix, and provide a controlled release continuing too few days [138]. The co− administration of lipids with drugs can also influence their absorption pathway though most orally administered compounds increase entrance to the systemic circulation via the portal vein, some extremely lipophilic drugs are transported straight to the systemic circulation via intestinal lymphatic's, which increases oral bioavailability of poorly soluble drugs [139]. Though, there are prominent hurdles confronting the SLNs (Fig. 5.19) [140].

Meng K et al., formulated docosanoic acid SLNs (DAS), octadecanoic acid SLNs (OAS), hexadecanoic acid SLNs (HAS), and tetradecanoic acid SLNs (TAS) and evaluated for intracellular delivery, accumulation, and discrepancy in antimicrobial efficacy of their loaded enrofloxacin by using RAW 264.7 cells. The SLNs prepared with longer fatty acid loaded enrofloxacin eliminated more slowly and accumulated in the cells for a longer time. The bactericidal activity of the four fatty acid SLNs aligned with intracellular Salmonella CVCC541 considerably improved compared to the free enrofloxacin. These results discovered that fatty acid SLNs, particularly docosanoic acid nanoparticles, may be efficient nanocarriers to ferry enrofloxacin or other lipid soluble drugs into cells for intracellular bacterial infection therapy [141]. Mukherjee S et al., developed glyburide loaded glyceryl monostearate solid lipid nanoparticles (Glb-SLNs) to improve the drug's solubility and oral bioavailability. Furthermore, it was evaluated for anti-diabetic activity in rats. *In vivo* results discovered that the treatment with SLNs of glyburide (Glb-SLNs) normalized blood glucose levels and serum biochemical parameters as compared with those of STZ controls. The shielding effect was additional confirmed by histopathological examination of the liver. These animals showed a comparable histopathological regeneration on Glb-SLNs treatment. These encouraging results confirmed the accomplishment of the proposed SLNs approach in enhancing glyburide oral bioavailability and confirmed its potential as an effectual system for diabetes treatment [142]. Khatak et al. formulated anti-tubercular drugs (Rifampicin, Isoniazid and Pyrazinamide) loaded solid lipid nanoparticles (ATDs-SLNs) using stearic acid, Compritol 888 ATO, and equal ratio of poloxamer 188: sodium taurocholate (% w/w). The *in-vitro* drug release study confirmed that the release of drug from SLNs was slow in assessment to marketed formulation and pure ATDs. Cytotoxicity of the ATDs-SLNs was

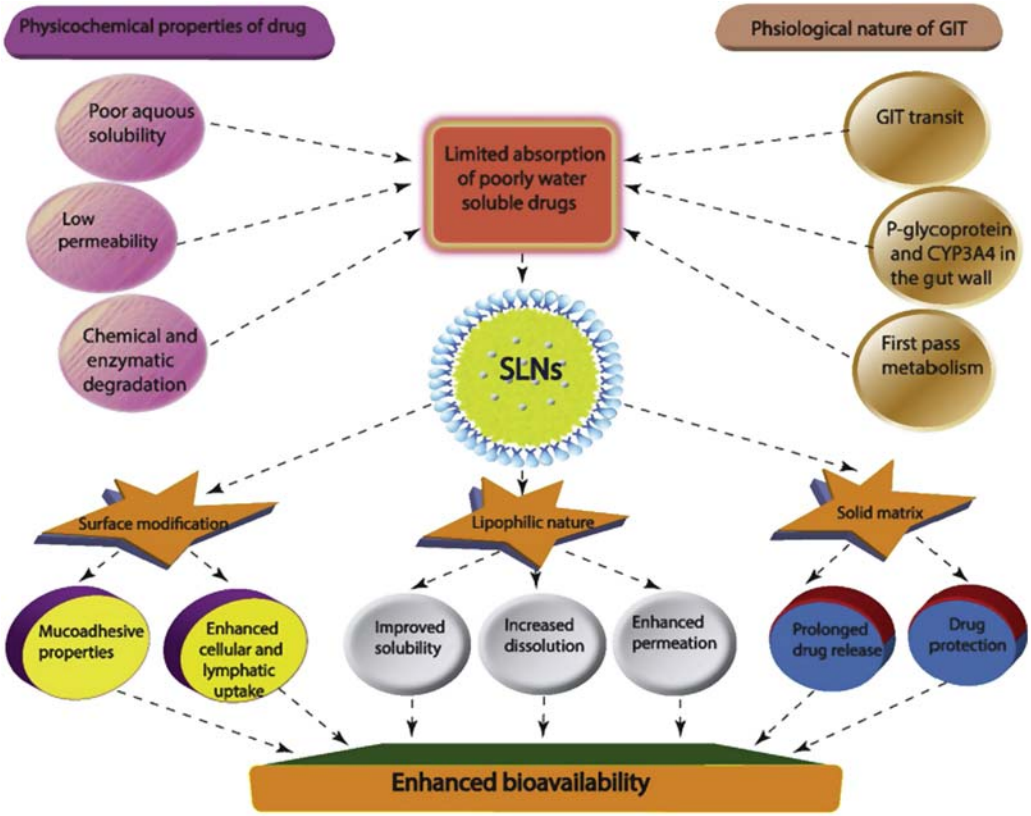

Figure 5.19

Schematic representation of the pitfalls of oral drug delivery and SLNs as a promising nanocarrier in the effective delivery of poorly soluble drugs. *From Copyright, 2020, Elsevier E. Salaha, M.M. Abouelfetouh, Y. Pana, D. Chena, S. Xie, Solid lipid nanoparticles for enhanced oral absorption: a review, Colloids Surf., B 196 (2020) 111305. https://doi.org/10.1016/j.colsurfb.2020.111305.*

premeditated on murine macrophage cell line (RAW 264.7) using modified MTT assay confirmed two folds growth inhibition of *M. marinum* as compared to standard antitubercular drugs. In general, the developed SLNs may be measured as a potential anti-mycobacterial nano-drug, providing a new direction to the tuberculosis clinics [143].

2.6 Others

2.6.1 Antibody nanomaterial conjugates

Nanoparticles by themselves suggest specific physicochemical properties that they do not show in bulk form where the materials show stable physical properties regardless of their sizes. Those properties create nanoparticles applicable in many biomedical applications. The conjugation of diverse moieties to the nanoparticles widens their application fields and

provides them with new or improved properties. A variety of biomoieties can be conjugated to the nanoparticles together with low molecular weight ligands (folic acid, thiamine, dimercaptosuccinic acid), peptides (RGD, LHRD, antigenic peptides, internalization peptides), proteins (BSA, Tf, antibodies, lectins, cytokines, fibrinogen, thrombin), polysaccharides (hyaluronic acid, chitosan, dextran, oligosaccharides, heparin), polyunsaturated fatty acids (palmitic acid, phospholipids), DNA, plasmids, siRNA, and thus forth. The conjugations of nanoparticles with antibodies combine the properties of the nanoparticles themselves with the specific and discriminating appreciation capability of the antibodies to antigens. As well, the development in the cellular uptake as well as the major intracellular stability might be two of the major advantages of using antibody conjugated nanoparticles [144]. Herda et al. adopted a methodology using antibody fragments conjugated to gold nanoparticles (immunogold) to map the available epitopes on a Tf grafted silica particle ($SiO_2-PEG8-Tf$) as a proxy method to expect nanoparticle biological function, and hence cellular receptor engagement [68]. They observed that the epitope convenience of SiO2−PEG8−Tf particles is low (approximately 4%). Though PEG length control and ligand layer architecture can improve this somewhat ($\sim$10%), the overall impression is that standard methods currently in use to graft targeting ligands may lead to quite poor (and heterogeneous) outcome. An increase in the Tf fraction labeled by IG, from one to $\sim$4%, was experiential by increasing the Tf density grafted on the particle surface. These results recommend that the grafting methodology has the greatest impact on epitope accessibility. Improving the design of surface ligand architecture might potentially address some of the challenges in the convenience and functionality of bionanoparticles [145].

Howard et al. developed actively targeted nanomaterials and exemplified using PEG-functional nanostructures coupled to a BsAb with dual specificity for methoxy PEG (mPEG) epitopes and cancer targets such as EGFR. The binding of BsAb-HBP bioconjugate to EGFR on MDA-MB-468 cancer cells is investigated in vitro using a fluorescently labeled polymer, and in *in vivo* xenograft models by small animal optical imaging. They found that antibody-targeted nanostructures demonstrated enhanced accumulation in tumor cells compared to non-targeted nanomaterials [146]. Kroll reported on the fabrication of a biomimetic, nanoparticulate anticancer vaccine that is capable of delivering autologously derived tumor antigen material together with a highly immunostimulatory adjuvant. They studied the antitumor therapeutic effect; C57BL/6NHsd mice were first administered on the right flank with 5×104 B16−F10 cells on day 0. On days 1, 2, 4, and 7, mice were vaccinated subcutaneously in the same flank with 200 μL of the nanoparticulate formulations. Kroll demonstrated the interaction of the nanoformulation with antigen presenting cells, bone marrow-derived dendritic cells was in use. While incubated with dye-labeled CpG-CCNPs, quick uptake was experiential until saturation was achieved at $\approx$6 h [147]. Haghighi AH et al., was intended to develop a

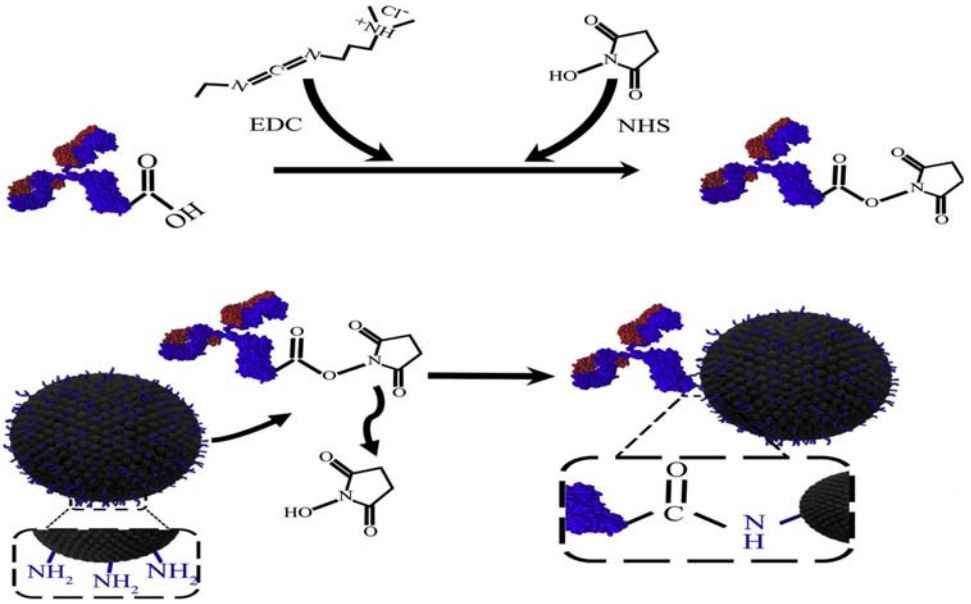

Figure 5.20
Schematic of antibody immobilization on the surface of amine-modified magnetic nanoparticles via EDC/NHS chemistry. *From Copyright 2020, Elsevier A.H. Haghighi, A.T. Khorasani, Z. Faghih, F. Farjadian, Effects of different quantities of antibody conjugated with magnetic nanoparticles on cell separation efficiency, Heliyon 6 (4) (2020) e03677.*

strategy to modify the magnetic nanoparticles surface with amine groups sequentially to make potential conjugation with the C-terminal region of Abs via ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC)/N-hydroxysuccinimide (NHS) chemistry (Fig. 5.20). They evaluated the effect of different amounts of Abs on the surface of magnetic nanoparticles on the separation efficiency of HER2+ breast cancer cells (SK-BR-3) to verify the optimal amount of anti-HER2 for conjugation without compromise antigen-capturing activity, with an observation to devise cost-effective immunomagnetic platforms [148].

2.6.2 Aptamer-nanomaterial conjugates

In conventional drug delivery systems lacking specific ligands, the drug diffuses in the entire body by systemic blood circulation lacking any specific mechanism facilitating accretion at the desired site of action. Under most situations only a small quantity of therapeutics reaches the target organ [149]. Targeted drug delivery is a preferred method for drug administration that increases the concentration of the drug at the desired sites of action, while leaving other tissues of the body unaffected. Consecutively to get specific delivery at the desired site of action, the surface of the particles has to be modified with a

targeting molecule [150]. This might be an aptamer, antibody, peptide or protein. Based on their high affinity and specificity, aptamers can be used as targeting ligands in a wide range of applications with affinity separation, analytics and cell targeting. Aptamers are short single-stranded or double-stranded RNA/DNA molecules which are capable to detect cell-specific molecules like receptors present on the cell surface with a high selectivity. In contrast to antibodies, aptamers have a high stability, a straight forward modification possible and be deficient in immunogenicity [151]. Gao et al. was prepared a targeted drug delivery system which consists of mPEG-PCL, HOOC-PEG-PCL and maleimide-PEG-PCL (MAL-PEG-PCL) and is functionalized with an aptamer (AS11411) and a 12-amino acid peptide. The AS111411 aptamer binds to necleolin, which is an extremely expressed protein in the plasma membrane of cancer cells like glioma cells. The TGN peptide is preferred by an in vivo phage display screening and allows modified nanoparticles the easier penetration of the blood brain barrier compared with the native phage [152]. Modrejewski investigated the cytotoxicity and specificity of drug-loaded and aptamer-functionalized nanoparticles, drug loaded NPs and only NPs (PEG-PCL-S15 (PTX), PEG-PCL-S15, PEG-PCL-S6 (PTX), and PEG-PCL-S6 A549 by incubating with HeLa cells. The results confirmed specific delivery and cellular uptake into A549 cells for S15-modified NPs. S6-modified particles were not able to deliver the included drug into A549 cells most probable as the aptamers molecular target does not facilitate endocytosis [153]. Chen et al.(2018)., constructed sali-entrapped lipid-polymer nanoparticles labeled with CD133 and EGFR aptamers (CESP) to target both osteosarcoma cells and CSCs. CESP in vivo exhibited the most excellent efficacy in inhibiting tumor growth than other controls in osteosarcoma-bearing mice. Therefore, CESP was confirmed to be proficient of efficiently targeting both osteosarcoma CSE and cancer cells. Fig. 5.21, Shows the mechanism of the targeting efficiency of CESP in osteosarcoma cells. As per the flow cytometry analysis of osteosarcoma cells, they found that osteosarcoma cells did not demonstrate homogeneous expression of antigens, and they consisted of 4 cell populations (EGFR+/CD133+, EGFR-/CD133-cells, EGFR+/CD133-, and EGFR-/CD133+). Owing to the negative expression of EGFR and CD133 in EGFR-/CD133-cells, ESP, CSP, and CESP did not exhibit increased targeting compared with SP (Fig. 5.21A). In EGFR+/CD133-cells, CESP exhibited amplified targeting compared with CSP, and similar targeting to ESP, which could be explained by the positive EGFR expression and negative CD133 expression (Fig. 5.21B). CESP exhibited improved targeting compared with ESP and similar targeting to CSP, which could be explained by the positive CD133 expression and negative EGFR expression in EGFR-/CD133+ cells (Fig. 5.21C). Considerably, CESP exhibited improved targeting compared with CSP and ESP, which could be explained by the positive EGFR and CD133 expression in EGFR+/CD133+ cells (Fig. 5.21D) [154].

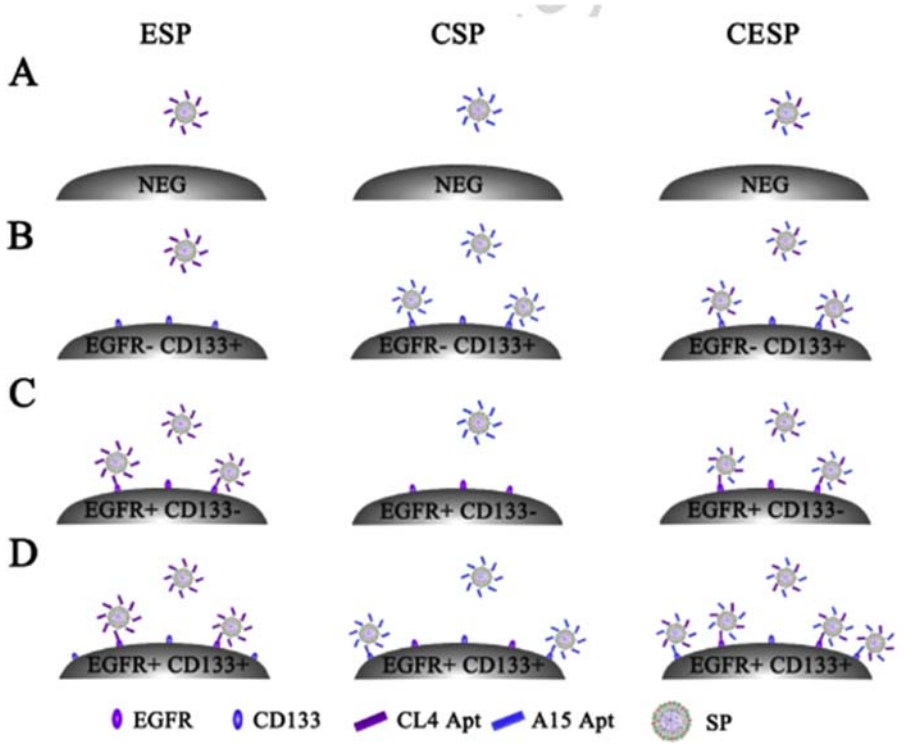

Figure 5.21

The mechanism of the targeting efficacy of CESP in osteosarcoma cells. (A) CESP, CSP and ESP do not target EGFR-/CD133-cells (CD133 and EGFR are negatively expressed). (B) CESP shows similar targeting to EGFR+/CD133-cells (EGFR is positively expressed, but CD133 is negatively expressed) as ESP, but increased targeting than CSP. (C) In EGFR-/CD133+ cells (EGFR is negatively expressed, but CD133 is positively expressed), CESP shows similar targeting as CSP and increased targeting than ESP. (D) CESP shows increased targeting to EGFR+/CD133+ cells (both EGFR and CD133 are positively expressed) than CSP and ESP. *From Copyright 2018, Elsevier F. Chen, Y. Zeng, X. Qi, Y. Chen, Z. Ge, Z. Jiang, X. Zhang, Y. Dong, H. Chen, Z. Yu, Targeted salinomycin delivery with EGFR and CD133 aptamers based dual-ligand lipid-polymer nanoparticles to both osteosarcoma cells and cancer stem cells, Nano 2018 (2018). https://doi.org/10.1016/j.nano.2018.05.015.*

2.6.3 Bacterial inclusion bodies

A main impediment to the marketing of recombinant protein drugs is the incidence of different stresses in the producing cells that results in proteolytic instability of recombinant polypeptides and/or aggregation [155], plummeting the yield of the soluble protein or restrictive its stability at midstream or even at postproduction stages [156]. In bacteria, the most explored cell factory for protein production, recombinant polypeptides often aggregate (partially or totally) as refractile and insoluble clusters called IBs. This is a result amyloids drug delivery inclusion bodies nanostructured materials therapy of the

non-physiologically high amounts of foreign polypeptides accumulates in the factory cell, which is inclined to cross-interact. As a consequence of this, IBs are formed as spherical or slightly ovoid proteinaceous particles ranging between 50 and 700 nm in size that are highly enrich with the recombinant protein and also contain minor amounts of cell proteins (mainly chaperones), traces of nucleic acids and other cell components. Microbiologists have explored a spectrum of approaches to minimize IB formation and thus increase the acquiesce of the soluble protein. Reducing the bacterial culture temperature, fusing peptidic tags to favor protein solubility or co expressing chaperone genes along with the target gene show irregular property that are highly product-dependent and not suitable for general application. Upon cell wall disruption, IBs remain stable and residue with the insoluble cell fraction. These particles can then be easily purified by frequent centrifugation and washing steps, upon enzymatic cell lysis or mechanical cell disruption. Since of the relative purity of the recombinant protein within IBs, the mechanical stability of these particles, their simple separation from cell debris and the cost-effective IB isolation processes, isolated IBs may be used as a convenient source of recombinant protein that can be improved in vitro, in soluble form, upon the application of protein denaturation and refolding treatments. In spite of the belief that IBs were composed of misfolded and nonfunctional versions of the target protein [157], recent research on the physiology of IB formation has exposed as a general trait, that at least a significant fraction of IB polypeptides are biologically functional and therefore properly folded [158]. Fascinatingly, mammalian cells in contact with purified IBs do not show any sign of toxicity. This information combined with the biological activity of IB proteins, encouraged us to discover the potential healing effects of IBs formed by therapeutic proteins, when added to the culture medium as "nanopills' for protein replacement [159]. As well, IBs formed by the therapeutic proteins Hsp70, LIF, catalase and dihydrofolate reductase enlarged the viability of target cells challenged with different stresses [159]. This was indicative not only of functionality however, also of bioavailability of the IB-embedded proteins. How IBs of up to 400 nm cross the plasma and nuclear membranes while maintaining the cellular integrity is a question that deserves further analysis. As the morphology of IBs remains fundamentally unchanged once the biological effect was made apparent, this have to be associated to the slow release of functional protein monomers [159].

2.6.4 Nanofibers

Nanofibers as pharmaceutical preparations have been expansively researched in the delivery of active drugs, therapeutic proteins and gene delivery [160–164]. In drug delivery and regenerative medicine, nanofibers play a significant role in controlling drug release rate, regulating cell behavior, and regenerating injured tissues [165]. Nanofibers with diameters ranging from several nanometers to tens of micrometers are ideal due to the biomimicry of extracellular matrix [166]. In addition, electrospun fiber scaffolds recommend distinctive features including uniformity in fiber size, diversity in composition,

flexibility in assembled structure, and ease of functionalization with bioactive molecules, making them capable candidates as carriers for drug delivery and scaffolds for regenerative medicine [167]. The drug delivery systems prepared of electrospun nanofibers have been new horizons in drug delivery [168]. The latest a number of therapeutic agents includes small molecular drugs and biological substances such as antibiotics, proteins, DNA, RNA, growth factors, and living cells have been integrated to electrospun fibers throughout either encapsulation during electrospinning such as blended electrospinning, emulsion electrospinning, and coaxial electrospinning, or surface modification post-electrospinning [160,168]. The electrospun nanofiber are appropriate for, transdermal drug delivery, topical drug delivery and oral drug delivery, while short nanofibers/fragments are sufficient for local injection to diseased sites in a minimal invasive way [169,170]. Nanofibers have been explored for oromucosal drug delivery of among others small molecule drugs for local anesthesia [171], nanoparticles for vaccination [172], as well as insulin for transbuccal delivery [173]. Maleki et al. manufactured electrospun nanofiber meshes from mixtures of PVA and honey at diverse weight ratios, loaded with dexamethasone sodium phosphate as the anti-inflammatory agent. The release profile of both PVA and PVA/honey (80/20) nanofibrous mats was correspondingly establishing that honey does not have an important effect on the release behavior of the entrapped drug. From these findings, Maleki accomplished that the anti-inflammatory agents could be released at early stages of formulation application, while honey will maintain as a natural antibiotic to progress the wound dressing effectiveness to facilitate healing rate [174]. Maslakci et al. employed polymeric blends of PVP and dextran as drug carriers to encapsulate IBU and acetylsalicylic acid (ASA) through electrospinning. The electrospinning solution has been prepared by mixing the dissolved PVA solution (45 wt %) individually with 2 wt% dextran having diverse molecular weight (dextran T10/dextran T40) and 200 mM of IBU sodium salt/ASA. The obtained nanofibers have been thoroughly characterized through several techniques. The solubility studies revealed fast disintegration time of 147.5 ± 20.0 and 16.2 ± 8.3 for ASA and IBF encapsulated PVP/Dext T40 nanofibers, respectively. Additional their antibacterial efficiencies against the Gram-negative (*Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922) and Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6633) have shown the possessions only against Gram positive strains. Taking into account all the findings, the study provides a prospect to design the orally disintegrating films and antibacterial wound dressings [175]. Stie MB et al., fabricated chitosan/PEO nanofibers containing chitosan of various DDA (53%−96%) by electrospinning, their morphology characterized by SEM and explored the mucoadhesive properties of electrospun chitosan/PEO nanofibers especially for sublingual administration. They demonstrated that chitosan/PEO nanofibers possess strong adhesion to porcine sublingual mucosa ex vivo by measuring the work of adhesion and that the mucoadhesive properties primarily relates to extraordinary swelling properties of the chitosan/PEO nanofibers. Tissue sections of

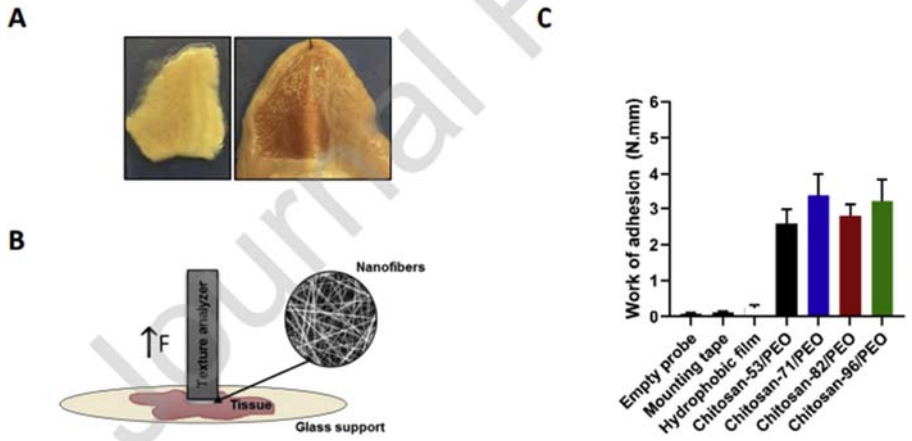

Figure 5.22

Adhesion of electrospun chitosan/PEO nanofibers to ex vivo porcine sublingual mucosa. (A) Tissue sections of ex vivo porcine sublingual mucosa were obtained using an electric dermatome. The images display a thin section of ex vivo porcine sublingual mucosa (left) and the ventral side of a porcine tongue after removal of the epithelium (right). (B) Experimental setup. The work of adhesion of chitosan/PEO nanofibers from ex vivo porcine sublingual mucosa mounted on a glass support was recorded by a texture analyzer. C) Work of adhesion of electrospun chitosan/PEO nanofibers with chitosan of various DDA (53%, 71%, 82% or 96%). The empty probe, mounting tape and a hydrophobic film were included as controls. Results are presented as mean ± SD. N = 4–5, *n* = 1–4, where *N* represents the number of biological repeats, and *n* is the number of measurements per individual tissue. *From Copyright 2020, Elsevier M.B. Stie, J.R. Gatke, F. Wan, I.S. Chronakis, J. Jacobsen, H.M. Nielsen, Swelling of mucoadhesive electrospun chitosan/polyethylene oxide nanofibers facilitates adhesion to the sublingual mucosa, Carbohyd. Polym. (2020). https://doi.org/10.1016/j.carbpol.2020.116428.*

ex vivo porcine sublingual mucosa were obtained by the use of an electric dermatome (Fig. 5.22A), and they were mounted on a glass sustain, and hydrated in isotonic buffer prior to analysis (Fig. 5.22B). Chitosan/PEO nanofibers showed strong adhesion to the sublingual tissue compared to the hydrophobic ethyl cellulose film (non-mucoadhesive control) (Fig. 5.22C). No differences were found in the adhesiveness of the different electrospun chitosan/PEO nanofibers irrespective of the DDA of the chitosan used [176].

3. Conclusions and future prospects

Each human is dissimilar an observance this in mind; perception of initialed medicine came into an emerald light almost a period of time. Same diagnosis and treatment may prime to diverse effects to different patients group. As various persons have altered genetic set up, hence drug response also varies. Extra problem of 21st century is emergent drug

resistance, wherever only a number of drugs are revealed in last 10 years; however a major number of antibiotics are now showing resistance. Due to the distinguishing properties of bionanomaterials, applying human use comprising catalysis, medicines, antimicrobials, biosensors, drug delivery and electronics. Bionanomaterials are presently being employed in pharmaceutical sciences as a novel drug-delivery system. Bionanomaterials in drug delivery may have dual functions for diagnosis and therapeutics. Nanomedicine has identified new techniques to treat life-threatening diseases. Though, there are some limitations, such as functionalized drugs being carried by individual nanoparticles are very much inadequate and their quantification is challenging. To accomplish the targeted DDS, conjugation of bionanomaterials with either an antibody or ligand is necessary. Nevertheless, the toxic effects of bionanomaterials necessity are taken into concern before using them in therapeutic applications. With increasing research on bionanomaterials in drug delivery and biomedicine, it can be expected that the knowledge of innovative bionanomaterials preparation strategies will be enhanced in the future. Forthcoming exertions are essential to design precisely targeting functionalized bionanomaterials to relieve adverse outcomes of chemotherapy. Furthermore, industrial developments in bionanomaterials formulations are desired to produce more efficient therapeutic or diagnostic agents to fight against cancer. However, further research is required before this new generation of bionanomaterials can become a reality.

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CHAPTER 6

Polymer-based bionanomaterials for biomedical applications

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1. Introduction

The use of nanotechnology is widespread in the delivery of drugs and is also expected to transform the future outlook of the biopharmaceutical industry. Nanotechnology can contribute to enhanced delivery of poorly water-soluble drugs, delivery of two or more drugs or therapeutic modalities for combination therapy, targeted delivery of drugs in a cell- or tissue-specific manner, endocytosis of drugs to intracellular sites of action, and visualization of drug delivery sites by combining therapeutic agents with imaging modalities and to improve the in vivo efficacy of the therapeutic agent [1]. Biodegradable and biocompatible polymeric-based nanomaterials are a promising option for drug targeting and sustained drug delivery. Nanoparticles vary between 10 and 1000 nm in diameter and have specific characteristics such as high surface-to-volume ratio, compact size, ability to encapsulate various drugs, and configurable surface chemistry. Due to their small particle size and superior encapsulation efficiency, they have been extensively used for drug delivery and drug targeting applications [2].

The selection of polymer is a crucial step, as it affects the drug release profile, drug loading capacity, drug bioavailability, and drug interaction with intracellular target sites. All these in turn influence the pharmacokinetics and pharmacodynamic attributes of the drug. The most important criteria in the selection of polymers include the interaction of the drug and polymer, along with polymer properties—molecular weight, loading capacity, and degradation profile. Polymers used for therapeutic purposes should be water-soluble or have the ability to form a stable emulsion and must be biodegradable, nontoxic, and nonimmunogenic. This chapter presents a comprehensive review of different types of polymeric bionanomaterials along with their multifarious biomedical applications (Fig. 6.1).

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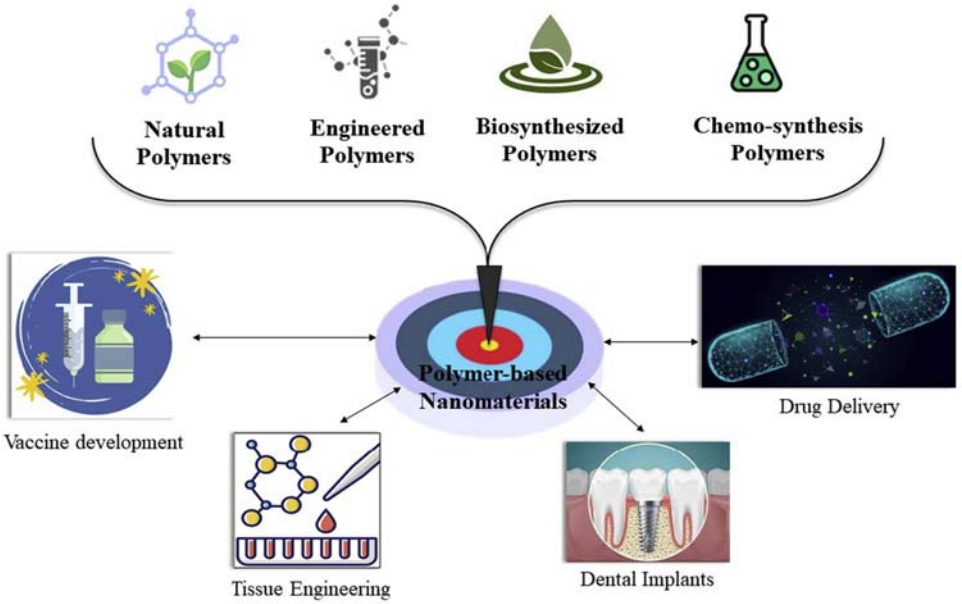

Figure 6.1
Polymeric nanomaterials and their biomedical applications.

The most common techniques used to design nanoparticles are categorized according to the physicochemical processes involved in their preparation, such as top-down, bottom-up, or hybrid techniques. In the top-down techniques, bulk polymers or suspensions are dispersed as smaller polymer nanoparticles. In bottom-up techniques, the polymerization of monomers leads to the creation of polymer nanocomposites. A combination of the top-down and bottom-up techniques called hybrid techniques offers some distinct advantages.

Biobased nanocomposites are composite materials made from renewable natural sources. These "nanobio" composites contain exotic, innovative, and interesting characteristics that make them a revolutionary environmentally friendly material. There is a significant research thrust to explore biobased nanomaterials with the primary objective of identifying substitutes to petrochemical-based polymers. Such bionanomaterials have been investigated for a wide range of biomedical applications such as drug delivery, tissue engineering, bioimaging, and biosensors. The discovery and identification of biomarkers for new diseases and related ligands have emphasized the importance of targeted drug delivery. This target-based drug delivery approach has been established for the treatment of critical diseases such as solid tumors, autoimmune disorders, and cardiovascular diseases (CVDs) [1]. The specific characteristics of nanoparticles include their potential to modify the pharmacokinetics and pharmacodynamic parameters of clinically used anticancer agents, thereby enhancing their therapeutic efficacy and providing a safer alternative to conventional anticancer therapy. A diverse range of materials organic, inorganic, protein, and lipid components are used to

design polymeric nanocomposites for drug delivery systems. Many therapeutic nanocomposites are approved by the US Food and Drug Administration (FDA) for clinical cancer treatment, and several others are under clinical trials. The use of nanocomposites in the treatment of CVDs is a comparatively new domain, and several findings have shown their ability to treat atherosclerosis [3]. Therapeutic management of ocular disorders is another growing field demonstrating the immense application of nanotechnology. Nanocomposites play a significant role in extending the residence time of ocular drugs, facilitating their penetration leading to better clinical outcomes.

2. Types of polymeric nanomaterials

2.1 Natural polymeric nanomaterials

Natural polymers are generated or derived from nature. They can be degraded to water, carbon dioxide, and small inorganic molecules and are categorized as eco-friendly materials. Natural polymers with a wide range of functional groups have been developed using physicochemical techniques or by modifying innovative materials using suitable nanotechnologies. The natural polymeric materials currently used are chitosan, starch, cellulose, alginate, albumin, and hyaluronic acid to name a few of them [4].

Chitosan is the most widely used polymer due to its superior biocompatibility and biodegradability attributes. It can form a bond with a negatively charged protein or a plasmid DNA via electrostatic interaction to form a polymeric composite, which prevents the degradation of protein and DNA [5] and hence can be used in biomedical applications. The presence of several amino and hydroxy groups in the chitosan scaffold makes it feasible for several chemical modifications [6].

Starch is present in cereals, potatoes, and beans. It is nontoxic, nonimmunogenic, highly stable, and noninteractive with drugs, and hence can be utilized in pharma sectors. It is used as a tablet excipient, a drug carrier, for bone and tissue repair, and as a protectant for plasma and frozen blood cells. The starch-based nanospheres display a wide surface area and limited adsorption efficiency, reduce equilibrium time of adsorption, therefore, and form a stable colloid and slow-release process. Hence, it is utilized as a drug carrier for sustained drug delivery systems [7–9].

Alginate is a natural polysaccharide derived by aquatic vegetation such as *Chlorophyceae, Cyanophyceae, Phaeophyceae, and Rhodophyceae* [10,11]. The commonly used alginate salts are ammonium alginate, calcium alginate, and sodium alginate [12]. The beneficial features of alginate include high absorption of moisture, high oxygen permeability, biocompatibility, biodegradability, and surface adsorption of metal ions making it ideal for medicinal use [13,14]. Table 6.1 describes the properties and potential applications of polymeric materials obtained by nature.

Table 6.1: Natural polymeric nanomaterials: properties and applications.

Materials	Properties	Applications
Chitosan	• A polysaccharide derived from chitin • Biocompatible, biodegradable, nontoxic, low immunogenicity allergic, and easily modified	• Orthopedic and periodontal applications • Tissue engineering • Wound healing • Drug delivery
Starch	• Low cost, degradation of simple and safe products • Nontoxic, nonantigenic	• Tissue engineering • Drug delivery carrier • Bone repair
Alginate	• A naturally produced anionic polymer derived from brown algae • Biocompatibility, low cost, and ease of gelation	• Drug delivery • Tissue engineering • Wound healing
Collagen	• Biocompatibility, biodegradability, and weak antigenicity • Develops fibers with enhanced stability and strength via self-aggregation and cross-linking	• Ophthalmic drug delivery systems • As sponges for burns/wounds • Minipellets and tablets for protein delivery • To formulate a gel in conjugation with liposomes • Sustained release drug delivery • Transdermal delivery and nanoparticles for gene delivery
Albumin	• The purest form of human serum protein • Selective delivery capabilities, nontoxicity, and nonimmunogenicity	• Brain and liver targeting • Tumor-targeted drug delivery
Hyaluronic acid	• A high-molecular-weight, nonsulfated anionic polysaccharide from the glycosamine glycan family • It is biodegradable, nontoxic, biocompatible, nonimmunogenic, and noninflammatory	• Used in skin rejuvenation • Drug delivery • Tissue engineering • Molecular imaging

2.2 Engineered polymeric nanomaterials

Engineered polymers are materials with extraordinary mechanical properties, such as stiffness, hardness, and low creep, which make them desirable for biomedical applications. These groups of polymers have better mechanical and/or thermal properties as compared

with natural polymers. Engineered polymers are expensive, hence manufactured in small quantities, and generally preferred for smaller devices or low-volume applications. Some examples of engineered polymers include polysulfones (PSfs), acrylonitrile butadiene styrene (ABS), and polyethylene oxide (PEO) to name a few.

PSfs have high mechanical strength, toughness, low creep rate, oxidation resistance, and good hydrolysis resistance. They provide high stability in aqueous inorganic acids, alkali, and salt solutions, rendering them a perfect candidate for biomedical applications [15]. PSfs are mainly used in tissue engineering and bone implantation due to their beneficial attributes [16].

ABS is a copolymer synthesized by polymerizing acrylonitrile and styrene in the presence of butadiene. It has high mechanical strength, is relatively cheap, and hence is commonly used in 3D bioprinting and cartilage engineering [17].

Polyimides are thermoset polymers that have excellent thermal, electrical, mechanical, and chemical resistance properties. They exhibit beneficial features such as biocompatibility, high tensile strength, transparency, low friction, thin walls, high tolerance, flexibility, and column strength. It satisfies ISO 10993 biocompatibility requirements for class III devices and can therefore be used in medical applications such as cardiovascular catheters, angioplasty, stents, drug delivery devices, and neurological devices [18].

Polyethylene glycol (PEG) also known as PEO is a nontoxic, biocompatible, and water-soluble material that can be used for medical purposes [19]. PEG has been approved by the US-FDA as a pharmaceutical excipient and also as a carrier for controlled drug release and tissue engineering [20]. Table 6.2 describes engineered polymeric materials along with their properties and applications.

2.3 Biosynthesized polymeric nanomaterials

Biosynthesized polymers are produced by hydrolysis of an enzyme (utilizing microbial enzymes). Such materials include polysaccharides and microbial polyesters. The biosynthesized nanomaterials mainly include polyhydroxybutyrate (PHB), poly(3-hydroxybutyrate-co-3-hydroxy valerate) (PHBV), and polyamino acid.

PHB is a high-molecular-weight polymer formed by using microbes under adverse growth conditions [21]. An eco-friendly and novel solvent, a mixture, acetone/ethanol/propylene carbonate, was used to extract PHB from *Cupriavidus necator* with a recovery of 83% and purity of 90% [22]. PHB has favorable attributes of biodegradability, biocompatibility, piezoelectricity, and optical activity [23]. This large molecular polymer is used as a drug carrier, as a scaffolding material in tissue engineering, and as a bone repair material in surgical therapy. Chaturvedi et al. have shown that insulin-charged deoxycholic acid

Table 6.2: Properties and applications of engineered polymeric nanomaterials.

Materials	Properties	Applications
Polysulfones	• High strength, stiffness, low creep rate, oxidation resistance, good hydrolysis resistance • Stable in aqueous inorganic acids, alkali, and salt solutions	• Tissue engineering • Bone implantation
Acrylonitrile butadiene styrene	• Low cost and good mechanical properties	• 3D bioprinting • Cartilage engineering
Polyimides	• Excellent thermal, electrical, mechanical, and chemical resistance properties • Biocompatibility, high tensile strength, transparency, low friction	• Cardiovascular catheters • Angioplasty • Cardiac stents • Neurological devices and drug delivery systems
Polyethylene glycol	• Nontoxic, biocompatible, and water-soluble material	• Pharmaceutical excipient • Carrier for controlled release of drugs
Poly(ethylene terephthalate)	• Hard, stiff, biological, chemical, and dimensional stability • Biocompatibility	• Surgical suture • Anterior ligament prosthesis
Poly(tetrafluoroethylene)	• Chemically and biologically inert • Nondegradable, hydrophobic, high crystallinity • Hemocompatibility • Low elastic modulus and tensile strength	• Artificial vascular graft • Catheter and sutures

combined with PEGylated PHB copolymeric nanoparticles has raised the intestinal insulin absorption to have a sustained hypoglycemic impact after 24 h in in vitro and in vivo studies [24]. PHB is mainly used in suture surgery, for soft tissue repair, as a wound repair material, as vascular substitutes, and as blood bags [25].

PHBV is a biopolymer of microbial origin with excellent biocompatibility and biodegradability, making it a suitable replacement for petroleum-derived polymers [26]. The unique characteristics of PHBV such as good absorbability, reduced cytotoxicity, piezoelectricity, and thermoplasticity make it quite desirable for biomedical applications including the manufacture of cardiovascular stents [27], release and transportation of drugs [28], and absorbable surgical sutures [29]. Application in the field of tissue engineering involves the development of tissue biodegradable implants, patches, biosensors, and the manufacture of porous scaffolds that enable the healing of bone injury induced by diseases and disorders where traditional therapies are unsuccessful [30–32].

Polyhydroxyalkanoates (PHAs) are natural, biodegradable polyesters synthesized under unusual growth conditions by microorganisms as intracellular carbon and energy storage components. It is nontoxic, has excellent biodegradability and biocompatibility, and holds strong potential in drug delivery, tissue engineering, and replacement for implantable devices, namely sutures, patch repair slings, orthopedic pins, scaffolds, stents, and adhesion barriers [33]. Table 6.3 describes biosynthesized polymeric materials along with their properties and applications.

2.4 Chemosynthesis polymeric nanomaterials

Polymer nanomaterials are also synthesized chemically using diverse reactions. These include polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polyurethane (PU), poly(methyl methacrylate) (PMMA), polyester, polyvinyl pyrrolidone, synthetic rubber, and polyvinyl alcohol (PVA) to list a few. These find wide applications in medicine.

PLA and its copolymer are extracted from a source of raw materials with good biocompatibility and biodegradability properties. In addition, they are safe and nontoxic and approved by the Food and Drug Administration (FDA). They have useful attributes of strong mechanical strength, thermal formability, and elastic modulus, making them amenable for use in cartilage repair, bone tissue engineering, and as a drug carrier in sustained-release formulations. PLA is also used in controlled release formulations as it effectively broadens the dose [34], reduces dosing frequency and dose, enhances the drug's concentration, and reduces the side effects on the liver and kidneys [35].

PLGA is a synthetic copolymer with excellent biocompatibility and biodegradability and is utilized to fabricate nanospheres, nanoparticles, pellets, films, and implants [36]. PLGA

Table 6.3: Biosynthesized Polymeric Nanomaterials: Properties and applications.

Materials	Properties	Applications
Poly-β-hydroxybutyrate	• Biodegradable • Safe and nontoxic • Excellent physicochemical properties	• Drug carrier for delivery of drugs • Tissue engineering material
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)	• Biocompatible and biodegradable • Good absorbability, biological origin, low cytotoxicity, piezoelectricity, and thermoplasticity	• Fabrication of cardiovascular stents • Tissue engineering • Biodegradable implants
Polyhydroxyalkanoates	• Nontoxic • Excellent biodegradability and biocompatibility	• Drug delivery and tissue engineering • Replacement for implantable devices

copolymers are commonly used in drug-controlled release material, especially for the release of chemotherapeutic agents, polysaccharides, proteins, antibiotics, and peptides [37,38]. Jena et al. developed capecitabine-loaded PLGA nanoparticles in combination with Eudragit S100 by nanoprecipitation technique. The PLGA-based nanoparticles showed high cytotoxicity against HT 29 cell lines in comparison with the pure drug and can therefore be used as a sustained-release system to selectively target colorectal cancer cells [39]. Hence, PLGA is potentially used as a carrier for drug delivery.

PU nanomaterials have great blood, tissue, and biological compatibility along with good fatigue resistance, elasticity, and strength. This nanomaterial can be used in biomedical applications, for example, to manufacture artificial organs, catheters, and nanocapsules [40]. Recently, biodegradable PUs that are available include PU-derived oligosaccharides; PU-derived lignin, tannin, and bark; PU-derived cellulose; and PU-derived starch derivatives [41,42]. PU has great biological compatibility and is resistant to thrombosis; hence, it has a strong potential in biomedical applications. Table 6.4 describes chemosynthesis polymeric materials along with their properties and applications.

3. Biofunctionalized nanocellulosic materials

3.1 Nanocellulose-based biodegradable polymers

Nanocellulose-based nanocomposites are extensively studied due to their favorable reinforcing effect on nanoparticles in a series of polymeric matrices. In cellulose

Table 6.4: Properties and applications of chemosynthetic polymeric nanomaterials.

Materials	Properties	Applications
Polylactic	• Biocompatibility • Good mechanical properties • It is safe and nontoxic • Strong mechanical strength, thermal formability, and elastic modulus	• Antiadhesion materials • Patches and sutures • Drug carrier and tissue-engineered scaffold
Poly(lactic-glycolic acid)	• Biocompatibility • Biodegradability	• As absorbable suture • Drug carrier • Bone fixation and tissue repair
Polyurethane	• Good compatibility • Good fatigue resistance, elasticity, and strength • Low toxicity, nonallergic • Nonteratogenic • Noncarcinogenic	• Medical bandage • As excipient
Polymethyl methacrylate resin [43]	• Easy operation • Good biocompatibility	• As dental material • Bone fixation material

nanocrystal (CNC)—reinforced poly (styrene-co-butyl acrylate) latex nanocomposites, an increase was observed in shear modules of more than two orders of magnitude [44]. Natural polymers and varied biopolymers are used as biodegradable polymer matrices for the preparation of nanocrystal cellulose-reinforced bionanocomposites. Petrochemical-based polymers that are used as matrices for nanocellulose-reinforced composites include polypropylene (PP), polystyrene (PS), and polyethylene (PE) in the nondegradable polymer family. In this section, several typical biodegradable polymeric matrices are selected for the discussion of nanocellulose-reinforced composite systems, where various reinforcement surface-modified nanocelluloses are mentioned.

3.1.1 Nanocellulose/polylactic acid

The primary challenge to produce PLA is its fragile nature. The mechanical properties can be enhanced by coupling PLA and nanocellulose without impacting the transparency of PLA. Haafiz et al. formulated cellulose nanowhiskers (CNWs) in combination with PLA nanocomposites using solvent exchange and solution casting techniques. This reinforced nanocomposite showed improved thermal and increased mechanical properties [45]. Similarly, Wei et al. developed ester (canola oil fatty acid methyl ester)-combined CNC (CNCFE)/PLA nanocomposites to minimize the CNC hydrophilicity. The structural properties were modulated by altering the CNC loading [46]. Like these, Arjmandi et al. formulated cellulose nanowhisker/montmorillonite/polylactic acid (CNW/MMT/PLA) nanocomposites and assessed the impact of CNW on the characteristics of nanocomposites. Their results indicated that 7% CNW had the greater effect on PLA crystallinity, while 1% CNW led to the maximum tensile strength of the CNW/MMT/PLA composites [47]. Wu et al. combined poly (D-lactide) on the CNC surface by ring-opening polymerization and blended with poly(L-lactic acid) (PLLA) matrix to develop a nanocomposite with a fast matrix crystallization capability and better heat distortion resistance. The development of the PLLA/CNC stereo complex improved the phase distribution and tensile properties of nanofillers [48]. Luo et al. developed an innovative porous bacterial cellulose nanowhisker (BCNW)/PLA composite that can be utilized in drug delivery and tissue engineering [49]. The PLA-based nanocomposites have a wide application in the biomedical sector for promoting the commercialization of nanocellulose.

3.1.2 Nanocellulose/starch

The integration of nanocellulose into starch-based composites demonstrated excellent properties, such as abundance, renewability, biodegradability, reduced cost, and ease of development. It provides a nanometer effect, which enhanced the mechanical properties, elastic modulus, and Young modulus. Wang et al. prepared electrospun starch-based fibers using nanocellulose as a reinforcing filler and cationic starch as a binding agent to enhance the mechanical strength. Their studies indicated that nanocellulose cationic starch improved the tensile strength and intermolecular ionic bonding and reinforced the fiber

structure [50]. Ilyas et al. designed bionanocomposites films by blending sugar palm starch (SPS) and sorbitol/glycerol with specific nanofiller sugar palm nanocrystalline cellulose (SPNCC) compositions using a solution casting process. These SPS/SPNCC nanocomposite films resulted in high crystallinity, tensile strength, Young's modulus, and thermal and water resistance [51,52]. Fazeli et al. developed a thermoplastic starch (TPS) nanocomposite as matrix reinforced with cellulose nanofiber (CNF) by the chemomechanical process. The 0.4 wt% CNF-loaded TPS films resulted in an increment in the tensile strength and elastic modulus by 80% and 170%, respectively [53]. The potential use of starch-based nanocomposites includes their use as carriers for drug delivery that protects active proteins from digestion, as microcapsules for small molecules, and as a biodegradable film for food packaging applications [54].

3.1.3 Nanocellulose/chitosan

The integration of nanocellulose with chitosan-based polymers often increases the water resistance, tensile strength, elastic modulus, thermal stability, and Young's modulus due to better dispersion and interfacial interaction between chitosan and CNCs, CNFs, or BC. Sampath et al. prepared a semiinterpenetrating polymer network of hydrogel with better mechanical properties and remarkable sensitivity toward pH changes along with chitosan-reinforced CNCs. This CNC—chitosan hydrogel had high pH sensitivity and a maximal swelling ratio under acidic conditions, indicating their application in tissue engineering, pharmaceuticals, and drug delivery [55]. Xu et al. fabricated CNC/CS composites using dialdehyde nanocellulose (DACNC) and demonstrated an increase in the isocratic point and swelling ratio with an increase in the percentage of chitosan in the composites. An in vitro drug release study using theophylline as a drug demonstrated excellent controlled release behavior and can be utilized as a carrier for gastric-specific drug delivery systems [56]. Doench et al. developed noncellularized composites of chitosan (CHI) hydrogel filled with CNFs of the type nanofibrillated cellulose and proposed their utility for repair and regeneration of an intervertebral disk and annulus fibrosus tissue [57].

3.1.4 Nanocellulose/alginate

Alginate is a biomass-based matrix used to develop reinforced nanocellulose composites as part of the polysaccharide family. Zhang et al. incorporated sodium alginate into the CNFs produced from raw ramie fibers and prepared a nanocomposite scaffold using the freeze-drying technique. This combination altered the porous structure, the mechanical properties, and the swelling behavior of the composite demonstrating its application in tissue, engineering [58]. Deepa et al. prepared a nanocomposite film by dispersing 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)—oxidized cellulose nanocrystals (TOCNCs) into the alginate matrix. This composition improved the mechanical strength of the polymer and demonstrated the potential applications of bionanocomposites in several areas—their porosity and smoothness make them suitable for use as a scaffold in tissue

engineering, and their relatively high mechanical performance makes them suitable for many structural and packaging applications [59].

3.1.5 Miscellaneous reinforced nanocomposite materials

Sun et al. developed esterified CNF via single-step mechanochemical esterification using ball milling. This esterified CNF was then developed into a nanopaper via vacuum filtration. The resulting nanopaper offered a high degree of optical clarity and excellent moisture resistance [60]. Poly(ε-caprolactone)-combined CNWs were formulated using open ring polymerization [61,62], and the inclusion of nanofillers improved the thermomechanical characteristics of poly(ε-caprolactone). Hakkarainen et al. presented an important application of wound dressing of wood-based nanofibrillar cellulose. This nanofibrillar cellulose dressing can be quickly applied to the wound bed and removed from the wound skin on its own after healing. In vivo clinical studies on a burn patient showed that this nanofibrillar cellulose dressing to be a very promising material for skin graft donor site treatment as it adheres to the wound bed and detaches from the wound surface on itself after skin recovery making it highly effective in wound dressing applications [63].

3.2 Nanocellulose-based thermoplastic polymers

Thermoplastics are described as polymers that can be melted and reshaped almost indefinitely. They melt on exposure to heat and harden on cooling. Hence, they can be recycled mechanically. A large variety of thermoplastic polymers, such as PP, PE, PVA, PS, polyethylene terephthalate, and polycarbonate, are used to develop cellulose nanocomposites [64]. This nanocellulose enhances some of the characteristics of thermoplastic polymer matrices mentioned and discussed in this section.

3.2.1 Nanocellulose/polyvinyl alcohol

The mixture of nanocellulose and PVA is of immense utility to green bionanomaterial development. Jasmani et al. developed nanocrystalline cellulose extracted from *Acacia mangium* and incorporated it into PVA to make a CNC−PVA film by casting solution. This reinforced nanocomposite significantly increased the tensile strength of PVA film [65]. Enayati et al. evaluated the application of nanohydroxy apatite and CNFs in electrospun PVA nanofibers for bone tissue engineering. The inclusion of fillers decreased the rate of biodegradation in phosphate-buffered saline and increased the cellular activity of scaffolds [66]. As a result, the fibrous scaffold has promising tissue engineering applications.

3.2.2 Nanocellulose/polypropylene

PP-based reinforced nanocomposites can be used in biomedical applications due to their recyclability, improved mechanical properties, and low development cost [67]. Yakkan et al. prepared PP−cellulose nanofibril (CNF) and Fusabond hybrid composites via

twin-screw extrusion technique. These PP/CNF composites combined with coupling agents exhibited enhanced mechanical properties such as tensile strength, thermal stability, and Young's modulus [68]. Ludwicka et al. prepared a stable composite by combining bacterial nanocellulose and perforated PP mesh. The developed bionanocomposites exhibited improved tensile strength, elasticity, and loading capacity and can be used in hernioplasty, cranioplasty, or hard and soft tissue reconstructive surgery [69].

3.2.3 Nanocellulose/polysulfones

PSfs are tough and stable polymers at high temperatures, are resistant to compaction stress, and hence can be used under high pressure. It is stable in aqueous acids and bases, and nonpolar solvents due to its hydrophobicity. The mechanical properties can be improved by mixing PSfs with hydrophilic nanocellulose. Daria et al. prepared a nanocomposite mixed-matrix membrane composed of PSf and cellulose nanomaterials using immersion precipitation or vapor-induced phase separation techniques. It was demonstrated that the CNC contribution to PSf membrane properties and performances depends on membrane preparation technique, doping concentration, and casting thickness [70].

3.3 Porous nanocellulose composites

The nanomaterials of high porosity, specific surface area, and low-density nanomaterials, sponge, foam, and aerogel materials are mainly developed by extracting liquid molecules via freeze-drying or supercritical CO_2 drying technique. This technique helps the liquid molecule dry slowly without affecting the solid matrix [71]. Nanocellulose can be used either on its own or in composites to make these porous materials. Studies for producing nanocellulose-based porous materials may usually be categorized as pristine nanocellulose-based aerogels, modified nanocellulose-based aerogels, and nanocellulose-based aerogel templates. Pristine nanocellulose-based aerogels are usually accessed by freeze-drying or by supercritical CO_2 drying techniques, leading to a lightweight final product [72–75]. Modified nanocellulose is utilized for the development of functional aerogels via surface modification, like surface physical modification with a hydrophobic coating to control oleophobicity [76] or adsorption [77], surface chemical modification for the removal of pollutants [78–80], surface chemical modification with a maleic acid cross-linking or self-cross-linking for the absorption of water and its surface recovery [81], and surface chemical modification by polyethyleneimine (PEI) for drug release purpose [82]. Nanocellulose-based aerogels template is a modification of nanocellulose-based aerogels, which has a unique characteristic to incorporate inorganic particles into the nanocellulose, for example, the addition of silver nanoparticles for catalytic degradation and analytical detection [83], incorporation of metal nanoparticles for magnetic properties [84] or electrode materials [85], and introduction of carbon or graphene nanotubes to increase conductivity [86,87].

3.3.1 Composite foams

Composite foams are derived from polymeric matrices. Nanocelluloses (either CNCs or CNFs) improve the mechanical properties and thermal stability of the resultant foams. The freeze treatment parameters, such as slurry concentration and freezing rate, directly impact the microstructure and morphological characteristics of the composite foams. Studies conducted by Kohnke et al. have shown that composite forms made from biopolymer xylan and CNCs wherein the pore morphology of foams is governed by solidification conditions and the molecular structure of polysaccharides. With the reinforcement of CNCs, the mechanical properties of the composite foams increased by 3.6-fold in the compressive modulus compared with that of xylan foam [88]. Dagang et al. showed that biodegradable PVA composite foams supported by 30 wt.% CNFs significantly increased the mechanical strength and modulus, energy absorption, water resistance, and dimensional stability of the composite foams, due to the rigid and semicrystalline nature, and regular and compact pore structures of the CNF [89]. In addition, composite foams prepared by the melt compounding/foaming method frequently showed an increase in crystallinity due to nucleation of nanocellulose during melting and foaming steps.

3.3.2 Composite aerogels

Aerogels are porous solids containing 99.8% of the air in them and have an extremely low density, which makes the material much lighter in weight. Composite aerogels exhibit high compressive strength when CNCs are incorporated into the matrices. The most common CNC-enhanced composite aerogels include clay [90], whey protein [91], arabinoxylan [92], and polyimide-based aerogels [93]. Nguyen et al. developed polyimide-based composite aerogels with carboxylic acid−functionalized CNCs as a filler, which showed low shrinkage, low density, and high porosity for composite aerogels. In addition to high tensile modulus, the ability of nanofillers to aid the thermal stability of porous aerogel architecture is another key aspect of CNC-incorporated aerogel [94]. Hayase et al. developed a polymethyl silsesquioxane−CNF composite aerogel via sol−gel technique with these composite aerogels having low density, low thermal conductivity, bending flexibility, visible light translucency, and superior hydrophobicity [95]. Researcher Lu et al. prepared a composite aerogel derived from cross-linking of collagen and dialdehyde-modified CNFs. The collagen/CNF composite aerogels exhibited low densities (0.02−0.03 g/cm^3), high porosity (90%−95%), high water absorption up to 4000%, good biocompatibility, and a high level of cell proliferation and activity, which can be suitable for wound dressing and tissue engineering scaffolds [96]. Zheng et al. demonstrated that cross-linking of PVA−CNF composite aerogels resulted in higher absorption of different oils (e.g., crude oil) or organic solvents (weight gain ranging from 44 to 96 times of its dry weight) and showed an impressive scavenging capability for various types of heavy metal ions (e.g., Pb^{2+}, Hg^{2+}) [97]. Bacterial cellulose has also been documented as a raw

material for the preparation of aerogels or foams. It is mainly used as a template material to support inorganic or metal nanoparticles for the development of functional porous materials [98].

4. Bioinspired polymeric nanocomposites

A major focus of hydrogel research is to develop a 3D microenvironment that can promote cell proliferation and differentiation. The implanted material is anticipated to perform several functions such as mechanical stability, cytocompatibility, and bioactivity, but most pure single polymer systems are unable to meet these requirements, making the development of bioinspired nanocomposite networks important and useful (Fig. 6.2). Therefore, we focus on those bioinspired polymer-based nanocomposites [99].

4.1 Polymeric nanocomposite hydrogels

Nanocomposite hydrogels are extremely hydrated 3D polymeric matrices filled with nanoparticles. These water-swollen polymeric networks conjugate with a biomimetic microenvironment, to increase cell viability in vivo by hydration, and facilitate the

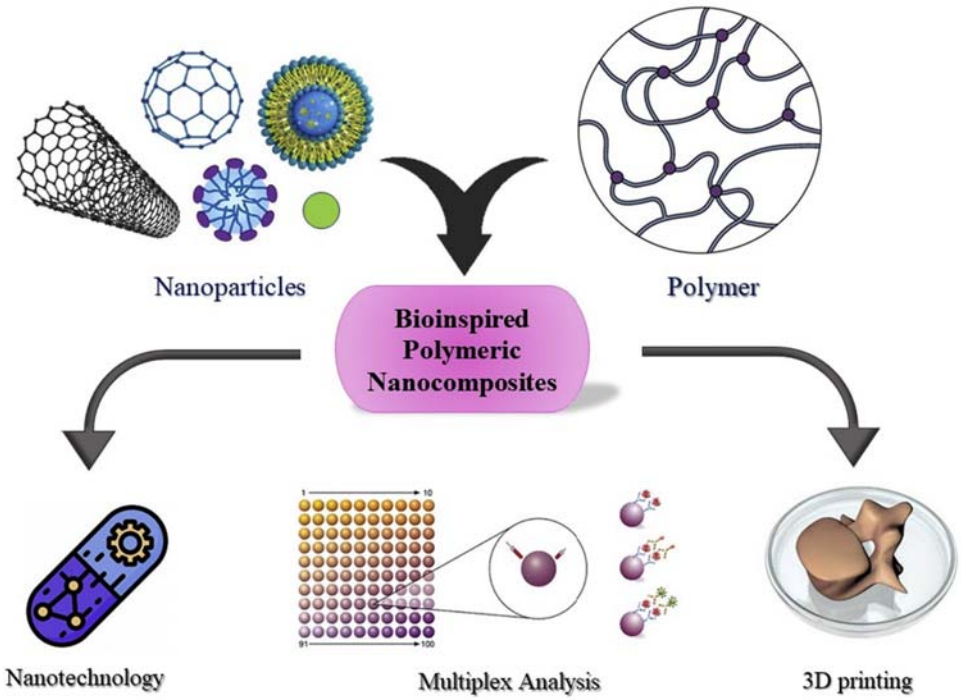

Figure 6.2
Bioinspired polymeric nanocomposites.

diffusion of nutrients and waste to an encapsulated cell population. The development of a hydrogel with suitable mechanical stability and bioactivity continues to be a challenge [100−102]. A variety of hydrogels are reported to be synthesized using natural and synthetic polymers to imitate natural tissue structure and physical properties [103]. Eventually, a variety of nanoparticles have been incorporated into the polymeric network to provide bioactivity, electrical conductivity, and stimulation responsiveness [104]. Giri et al. designed a nanocomposite based on carboxy methyl guar gum (CMG) and chemically modified multiwalled carbon nanotubes (MWCNTs) for sustained transdermal release of diclofenac sodium. In this study, the nanoparticles provide excellent thermal stability, increased drug loading capacity, and enhanced drug retention efficiency within the hydrogel [105]. Bozoglan et al. developed thermosensitive chitosan/carboxyl methylcellulose/scleroglucan/MMT nanocomposite hydrogels that showed improved gelling temperature and thermal stability of the hydrogel. The results indicated these hydrogel materials to have potential application in tissue engineering, drug delivery, and wound dressing [106]. Nanocarbon nanofillers (graphene, nanodiamonds, carbon nanotubes [CNTs], and fullerene C_{60}) have been embedded in polymeric hydrogels to obtain high-performance materials [107]. These polymer-based hydrogel nanocomposites may be pH/temperature/concentration/light-sensitive and can function as good drug carriers for controlled drug delivery. Despite significant advancement in the science of the development of nanocomposite hydrogels, there is a lack of sufficient information on their long-term in vivo cytotoxicity, stimulus sensitivity, biodegradation, and mechanical properties [108], which expands the research landscape of polymeric nanocomposite hydrogels.

4.2 Bioactive silicate-based nanocomposites

Synthetic silicates are a new category of ultrathin nanomaterials with a high degree of anisotropy and functionality that interact with biological entities in a different way owing to their high surface-to-volume ratio with their respective 3D nano-, micro-, and macrocounterparts [100,109]. This silica-based material is prepared via sol−gel, melting, sintering processes, and powder technology. The rapid and progress in the development of ultrathin nanomaterials opened new vistas in biomedical application in areas of therapeutics, imaging, and diagnosis. These synthetic silicates can strongly interact with the stem cells and induce osteogenesis without using any external osteoinductive factor [110,111]. Cells have been effectively internalized through cadherin-mediated endocytosis because the silicate-based nanocomposite is disc-shaped and charged on the surface. These nanoparticles, on internalization, upregulate the osteorelated genes and proteins, such as RUNX2, osteocalcin, and osteopontin, leading to the development of mineralized ECM [110]. Recent studies indicated that the performance of biocomposite nanomaterials can be

improved by incorporating silicate-based nanoparticles (such as bioactive glasses and glass ceramics) in the field of tissue engineering [112]. In particular, bioactive glass nanoparticles play a significant role in the expression of osteoblast gene cells and potential angiogenesis that provide an environment for cell growth, proliferation, and differentiation [113,114]. In addition, silicate-based nanocomposites also hold promise in wound healing applications [115−117]. The incorporation of inorganic materials into these nanocomposites enhanced their mechanical stability and promoted the wound healing process by providing a therapeutic effect [117].

4.3 Bioinspired hydroxyapatite nanocomposites

Nanohydroxyapatite (nHAp), a mineral that is naturally contained in hard tissue, is another potential candidate for incorporation as a bioinspired nanofiller [118]. Shakir et al. fabricated a nanohydroxyapatite/chitosan-tamarind seed polysaccharide (n-HA/CS-TSP) nanocomposite via the coprecipitation method. The strong interaction between these three components provided the most porous and rough surface and increased thermal stability, compressive strength, and modulus, making it a promising biomaterial in bone tissue engineering [119]. In clinical dental and orthopedic applications, the use of nHAp as a biomaterial is limited to nonstressed brimming regions due to its long-lasting characteristics and reduced fracture strength. Consequently, for non−load-bearing applications, nHAp has been merged into a polymeric hydrogel network [120].

4.4 Bioinspired Rosette Nanotube composites

Rosette nanotube (RNT) composites are derived from the assembly of synthetic DNA bases, primarily the hydrogen bonding pair between guanine and cytosine [121,122]. RNTs are used to encapsulate and deliver hydrophobic drugs often difficult to deliver in biological systems because of their amphiphilic character and hollow architecture. Another benefit of the use of RNTs for drug delivery is their biocompatibility, low cytotoxicity, and ability to establish a favorable, biologically inspired cell adhesion and growth environment [123]. RNT-coated titanium has many attractive attributes for use as vascular stent coatings, including spontaneous self-assembly in body fluids, flexible surface chemistry for different implant applications, and nanoscale dimensions close to those of the natural extracellular vascular matrix [124].

4.5 Graphene-enhanced polymeric nanocomposites

In a hybrid design approach, 2D nanomaterials such as graphene can be combined with 3D polymeric hydrogels or tissue engineering scaffolds because their unique shape and

surface properties promote cell activity and stability. Graphene oxide sheets are self-assembled by noncovalent interactions with single-strand DNA creating 3D structures [125]. Linear low-density polyethylene (LLDPE) nanocomposites with thermally reduced graphene were developed by melting and showed a high increase in tensile modulus, stress breakage, and tensile stress [126,127]. The incorporation of graphene into polymer chains enhanced the mechanical and/or electronic properties [128]. Polymeric composites of graphene oxide—coated particles are used in dopamine detection, monitoring of mammalian nervous cells, proteins, and *Escherichia coli* cells [129]. Konwer et al. reported that methanol-sensitive nanocomposites with enhanced polyaniline (PANI)—graphene oxide characteristics were used to amplify colorimetric sensors for target DNA detection as PANI resistance was increased when exposed to methanol vapor due to the strong hydrogen bonding between methanol and the polymer chain [130].

4.6 Polymeric nanocomposites loaded with metallic nanoparticles

The incorporation of metal-based materials in polymer matrix provides a variety of pathways for responsive tissue regeneration. For example, metal nanomaterials have been incorporated into PLGA-based scaffolds and used as effective antimicrobial nanocomposites in hard tissue engineering with the benefit of improving bone regeneration [131]. Interactions between peptides and solid inorganic surfaces can engineer reorganized molecular structures for improved bioactivity, and further functionalization with synthetic materials improved the regenerative performance of the implanted device [132]. Additionally, the conductivity of gold nanoparticles embedded in a polymeric matrix or nanofiber renders them to be attractive to regenerative processes using electrical stimulation that mimics neuronal pathways [133,134]. Despite these developments, further research is required to gain a deeper understanding of the interactions between stem cells and organometallic composites and to develop stimulus-responsive materials that mimic physiological conditions.

4.7 Mechanically stiff interpenetrating networks

The majority of tissue components, such as cartilage and muscle, consist of several forms of polymers that result in the development of interpenetration networks. The various forms of IPNs are sequential, simultaneous, and semi-IPNs. The sequential IPNs are sequentially formed by more than one IPN in a process, while simultaneous IPNs are created simultaneously and semi-IPNs are formed by the polymerization of a monomer in the presence of a polymer [135]. The appealing characteristics of IPNs such as stability, swelling capacity, nontoxicity, biocompatibility, and biodegradability have generated immense interest in the pharmaceutical field, particularly in delivering bioactive molecules

to the target site [136,137]. Feig et al. developed highly conductive hydrogel with dual electronic and ion conductivity and highly tunable mechanical properties that mimic biological tissue. This combination of properties makes conductive-IPN hydrogels promising for application in implantable devices, for which the idea of combining high electronic conductivity with low modulus and high stretch ability is especially desirable in soft biological interfaces such as the brain [138]. Kim et al. developed a novel technique for preparing semi-IPNs made of chitosan and poloxamer. Their technique consists of photo-cross-linking the poloxamer macromer in the presence of chitosan using freeze-drying to obtain hydrogels of the sponge form. This IPN composite hydrogel showed rapid water adsorption, high mechanical strength, and interconnected pores that are suggested for wound dressing [139].

4.8 Spatially controlled hydrogel nanocomposites

Microfabrication methods, such as micromolding, can be used to regulate the cellular microenvironment to mimic native tissue microarchitecture and subsequent cell function in tissue engineering. A photothermally controlled gene delivery carrier is constructed by conjugating low-molecular-weight branched polyethylene (BPEI) and reduced graphene oxide (rGO) through a hydrophilic PEG spacer. This PEG−BPEI−rGO nanocomposite forms a stable nanosized complex with plasmid DNA (pDNA) along with enhanced gene transfection, resulting in a potential for spatial and temporal site-specific gene delivery [140]. The incorporation of spatial patterns on hydrogel surfaces enables the modulation of cellular activities in several ways, having significant ramifications for the therapeutic potential of hydrogel-based regenerative medicine [141]. Rio et al. developed a hydrogel device that encapsulated islet cells using the simple micromolding technique to restore normal glycemic levels in diabetic mice [142]. Gelatin methacryloyl hydrogel was developed by casting into a polytetrafluoroethylene mold and used for controlled release applications in an in vivo mouse model [143]. Additionally, replica micromolding has become a popular technique for producing low-attachment microwell arrays, cellular spheroids, and microorganoids that can be used to drive bottom-up tissue engineering to monitor stem cell activity and to enhance drug screening [144−148].

5. Biomedical applications

Recent innovations in polymer-based nanotechnology and nanoscience have undergone a revolutionary change in the development of new bionanomaterials with customized additional features that help in expanding the landscape of biomedical applications. These bionanocomposites are widely used for dental implants, drug delivery, stem cell imaging, tissue engineering, and as biosensors (Fig. 6.3) [149].

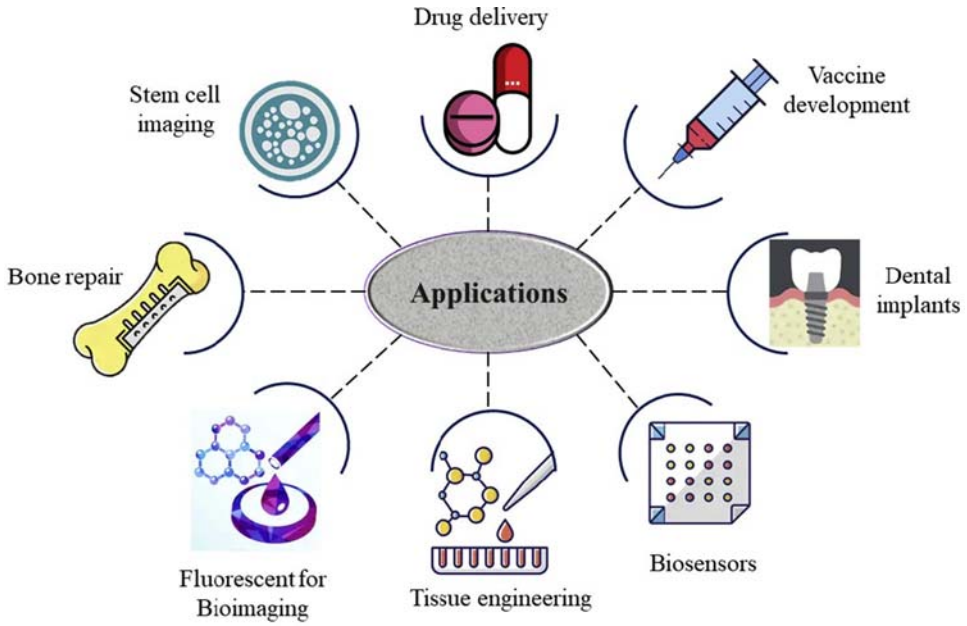

Figure 6.3
Biomedical applications.

5.1 Dental and biomedical implants

Traditional materials such as cement and dental amalgam have been replaced by polymeric materials and films due to their excellent physical, mechanical, and biological properties. These materials are used for dentistry regeneration and drug delivery [150]. The polymers used for dental applications are polycarbonate, PE, PEG, PU, PMMA, PLA, and hydrogels [151].

A critical challenge in dentistry is to prevent the formation of bacterial biofilms. Polymer bionanocomposites are therefore used to protect bacterial growth and biofilm formation on dental tissue. Nanoparticles are combined with antibiotics to deliver the drug to the target site by penetrating the biofilm and inhibiting microbial growth [152,153]. The prevention of microbial adhesion and its spread on dental surfaces relies on the relationship between the polymeric material and dental structure [154]. Jahanizadeh et al. prepared curcumin-loaded carboxymethyl starch/chitosan/MMT bionanocomposite and evaluated them for antimicrobial activity against *Streptococcus mutans*. This bionanocomposite effectively halted biofilm formation on dental surfaces [155].

PMMA is a synthetic polymeric material commonly used to develop different types of dentistry prostheses [156]. It is a tough, strong, lightweight material with good impact strength and environmentally friendly and stable as compared with other plastic polymers

[157]. The key role is to reduce biofilm formation and maintain good oral health. Various metallic nanoparticles of zirconium oxide, platinum, and silver are incorporated into PMMA to reduce microbial colonization. Incorporation of zirconium oxide with PMMA reduces the adhesion of *Candida albicans* to repair denture bases and interim removable prosthesis [158]. Different polymer films that are used as antimicrobials are applied to the prosthesis to prevent the formation of biofilm. Shibata et al. reported that poly(2-methacryloyl oxyethyl phosphorylcholine-con-butyl methacrylate) coating on a PMMA denture base inhibited the formation of sucrose-dependent *Streptococcus mutans* biofilm [159]. Silver nanoparticles (AgNPs) have been reported to exhibit antimicrobial properties that provide evidence for their application in dentistry [160]. Biocompatible antimicrobial agents combined with polymeric nanoparticles, therefore, produce an antimicrobial surface on dental prosthetics.

Titanium (Ti) surface provides good strength, nonreactive to the body, and growth of bone tissue, and hence is used for osseointegration in orthopedics and dental implants. Recent research in this area has focused on the design of bioactive coatings for dental implants to improve osseointegration by interacting with protein, tissue, and implant surfaces [161]. Studies have shown that biomimetic-coated Ti surfaces with nanohydroxyapatite and PLGA/collage nanofibers are used for dental implant surfaces to enhance the osseointegration process [162]. This coating material enhanced cell proliferation, cell adhesion, and mineralization on the implant surfaces. Shahi et al. synthesized tetracycline-containing fiber using tetracycline hydrochloride/PLA, poly(e-caprolactone), and gelatin polymeric solution [163]. These fibers inhibited the biofilm formation of periimplantitis-associated pathogens, such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Aggregatibacter actinomycetemcomitans*, and therefore suggested its application as an antibacterial film on dental implants [164].

5.2 Targeted drug delivery

Targeted drug delivery via the use of polymers has been at the center stage of many research initiatives as it improves the drug loading capacity of the polymeric drug carriers. The carrier enhances cellular uptake and releases drugs in a controlled manner at the target site. Das et al. developed a nanocomposite by cross-linking hydroxypropyl methyl cellulose/Au nanoparticles for colon-target drug delivery. Biodegradation studies were performed using hen egg lysozyme to confirm biodegradability. The study of c-HPMC/Au nanocomposite on human mesenchymal stem cells demonstrates noncytotoxicity. The swelling characteristics of different phosphate buffer media indicated the pH-responsive behavior of the hydrogel/nanocomposite. The synthesized hydrogel/nanocomposite released the colonic drugs (i.e., ornidazole and 5-amino salicylic acid) in a sustained manner [165].

Pan et al. developed a nanocomposite of a mixture of graphene oxide (GO), carboxymethyl chitosan, fluorescein isothiocyanate, and lactobionic acid (LA) for targeted delivery of doxorubicin. The drug was loaded onto this developed nanocomposite using an adsorption technique. Their results indicated that LA-containing composite induced cell death in cancer cells (SMMC-7721), while the LA-free analog was found to be inactive and can therefore be used for targeted anticancer drug delivery [166]. Kouser et al. formulated nanocomposite hydrogel films using carboxymethylcellulose–hydroxyethylcellulose–acrylonitrile-lined polyol (CHAP) plain hydrogel and Na-montmorillonite (NaMMT) dispersed CHAP nanocomposite hydrogel films (NaCHAP). The introduction of NaMMT in the CHAP matrix resulted in increased stability of nanocomposite hydrogels and induced hydrophilicity in swelling ratio measurement and tensile strength. The in vitro cytotoxicity of cisplatin-loaded nanocomposite hydrogels indicated that these films effectively inhibited the growth of human breast MCF-7 cancer cell line, thereby providing a viable platform for controlled anticancer drug delivery [167].

Gandara-Loe et al. prepared a metal–organic frame (MOF)–based polymer nanocomposite film and loaded it with an ocular drug (brimonidine). The drug embedded in polymer film showed prolonged drug release indicating its suitability for drug delivery in ocular therapeutics, either as a component of a contact lens, in the composition of lacrimal stoppers (e.g., punctual plugs), or subtenon inserts [168].

Several novel nanocomposite systems have recently been designed for cell-specific bone targeting improved drug solubility, drug stability, and inhibition of drug degradation to achieve better targeting. These targeting systems may comprise biological compounds such as bone marrow stem cells, growth factors, RNAi, parathyroid hormone, or synthetic compounds (bisphosphonates and calcium phosphate) [169].

5.3 Bionanomaterials for therapy of defective joints and bones

The use of nanotechnology in the development of novel biomaterials overcomes the limitation of long-term loss of implants, as nanomaterials show excellent biomimetic activity. Das et al. coated the surface of the titanium implant with a biodegradable, highly porous, osteogenic nanofibrous coating that enhanced its osteoinductive and osteoconductive properties. The coated implant showed new bone formation when placed on the tibia of the rabbit providing a novel approach to bone integration [170]. Wang et al. developed polyetheretherketone/nanofluoro hydroxyapatite (PEEK/nano-FHA) biocomposite that enhanced antibacterial activity and osseointegration and therefore can be used as bone implants [171].

Nejadnik et al. developed a hybrid nanocomposite consisting of bisphosphonate hyaluronic acid and calcium phosphate nanoparticles. These nanocomposites are capable of

self-healing and can be used in tissues or bone regeneration. It showed excellent biocompatibility, bone-to-implant interactions, and good adhesion to mineral surfaces such as enamel and hydroxyapatite [172] making it a promising material in the regeneration of bones and joints.

Sharma et al. designed a PEG diacrylate hydrogel to support cartilage matrix production, with the easy surgical application. This biomaterial demonstrated the deposition and development of cartilage tissue by mesenchymal stem cells in the joint regions. The adhesion of the implant to cartilage and bone tissue was achieved by a chondroitin sulfate adhesive covalently bonded to the hydrogel. This clinical study conducted on 15 patients showed that the implant significantly reduced knee pain with increased extracellular matrix tissue, thus promoting ligament and cartilage regeneration [173].

5.4 Bone tissue engineering

Polymer bionanocomposites play a significant role in tissue engineering and regenerative medicine. These nanocomposites are designed to create scaffolds that provide a 3D structure on which cells can differentiate and proliferate in an extracellular matrix and form functional bones or tissues [174]. It has been reported that CNTs combined with polymeric chitosan have resulted in excellent improvement in the mechanical strength of nanocomposites [175]. These CNTs have received great attention as potential bionanomaterials, especially those in contact with natural bones, such as prostheses used for arthroplasty, plates/screws used in fracture fixation, drug delivering systems, and bone regeneration scaffolds [176]. The main objective for the use of CNTs in biomaterials includes tissue safety and bone tissue compatibility. Studies on CNTs have shown that they exhibit effective bone tissue compatibility with the ability to mend bone when in contact with bone tissue that further accelerates the bone formation and stimulates bone morphogenetic protein [177]. However, the primary challenge in bone tissue engineering is to enhance the mechanical strength of the scaffold in such a way that it can be used effectively.

Nazeer et al. prepared an intercalated chitosan/hydroxyapatite (CS/HA) nanocomposite. Thermogravimetric analysis showed complete degradation of chitosan matrix that further led to the formation of nanoporous 3D scaffolds containing hydroxyapatite, β-tricalcium phosphate, and calcium pyrophosphate. The X-ray diffraction pattern and scanning electron microscopy data indicated the formation of layered nanocomposites [178], making this polymer nanocomposite an attractive and promising material for bone tissue engineering.

Li. et al. developed a bionanocomposites with polymeric matrices composed of synthetic biodegradable aliphatic polyesters combined with nanohydroxyapatite (nHA) and/or

graphene oxide (GO) nanofillers for bone tissue engineering. Synthetic aliphatic polyesters mainly include PLA, polycaprolactone (PCL), and copolymers of PLA−PGA. Such bionanocomposites are being studied to create 3D porous scaffolds for bone defect repair because nHA and GO enhance their bioactivity and biocompatibility by inducing biomineralization, bone cell adhesion, proliferation, and differentiation, therefore facilitating the formation of new bone tissue after implantation [179].

The recent design of porous scaffolds for bone tissue engineering was 3D printed using PLGA/TiO_2 composite (10:1 weight ratio). This composite improves the compressive modulus of the scaffold. The results indicated that scaffolds with PLGA/TiO_2 substantially increased the proliferation of osteoblasts relative to pure PLGA. In addition, osteoblasts cultivated on nanocomposite PLGA/TiO_2 displayed greater alkaline phosphatase activity and improved calcium secretion compared with pure PLGA scaffolds [180].

Prakash et al. developed chitosan/PVA/graphene oxide/hydroxyapatite/gold films for potential orthopedic applications. These biofilms were found to be biocompatible with mouse mesenchymal cells and enhanced differentiation of osteoblasts as indicated by more alkaline phosphatase activity at a cellular level. The results suggested that these nanocomposite films have an osteogenic potential in the treatment of bone and bone-related diseases [181].

5.5 Biosensor platforms

The biosensors are devices that are highly sensitive to identify and detect a target and are commonly used for diagnostic purposes in the medical field. These biosensors can detect a glucose molecule, biopolymer, such as protein or DNA, and bacterial organisms [182].

Xu et al. developed a robust enzymatic biosensor by coassembling glucose oxidase (GOx) with MWCNTs and amphiphilic copolymer poly(acrylic acid-r-(7-(4-vinyl benzyloxy)-4-methyl coumarin)-r-ethyl hexyl acrylate) (PAVE). This enzyme-loaded nanocomposite showed a necklace-like structure with GOx-containing polymer nanoparticles as nanobeads and MWCNTs as a long string through these nanobeads. Furthermore, the GOx@PAVE-CNTs bionanocomposites were electrodeposited to the electrode surface, and a robust biosensing complex film with a porous network structure was formed after photo-cross-linking resulting in the fabrication of a glucose biosensor. This biosensor showed a high glucose selectivity and specificity and can be used to detect glucose levels in human urine and serum samples with satisfactory results [183].

Dervisevic et al. designed a new electrochemical urea biosensor based on ferrocene-poly(amidoamine) (Fc-PAMAM) dendrimers incorporated with MWCNTs. The biosensor electrode was tested for reusability, storage, interference behaviors together with optimum

temperature, and pH parameters using a cyclic voltammogram. This electrode demonstrated excellent performance in the urea detection within a range of 0.2−1.8 mM, the detection limit of 0.05 mM, fast response within 3 s, and sensitivity of 1.085 μM/cm^2/mM. This biosensor when screened in healthy human blood samples for urea detection gave excellent selectivity and sensitivity proving its utility for urea measurement [184].

Recent literature reports indicate the fabrication of glucose biosensors by reinforcing glucose oxidase (GOx) inside the PANI−MMT−platinum nanoparticles (PtNPs) nanocomposite by in situ electrochemical suspension polymerization. The engineered biosensor showed a rapid response to glucose over a linear range of 10 μM to 1.94 mM and a low detection limit of 0.1 mM and can be successfully used to detect glucose in human blood serum [185].

5.6 Vaccine development

Different immunogens used in vaccine formulations require adjuvants to activate the immune response. Traditional adjuvants comprise various types of aluminum derivatives and emulsion, which may change their nature during preparation or after injecting into the body. For example, the droplet size may increase after injection into fatty tissues and cause the emulsion droplets to coalesce into larger particles. Aluminum hydroxide adjuvants are generally recommended for use in humans and animals for health reasons. Moreover, the only adjuvants used in FDA-licensed vaccines are based on aluminum. These adjuvants primarily induce the immune response of Th2 when injected into mice and activate the CD8T cells. Antigens adsorption to aluminum adjuvants boosts the immune response by promoting phagocytosis [186]. Hogenesch et al. demonstrated the preclinical safety of the *Streptococcus pyogenes* recombinant vaccine prepared with an aluminum adjuvant, and the results indicated that repeat-dose toxicity did not lead to any serious vaccine-associated adverse reactions in outbred CD-1 mice [186].

The main reason for using polymeric materials is that they are renewable materials and their particle size and components can be controlled. Nanoparticles comprise micronized or nanosized polymers that are used as a carrier for vaccines. Vaccine antigens are covered with particles via polymerization. These antigens are further bound to nanoparticles by adsorption to the surface of nanoparticles by chemical bonds. Zhao et al. developed a chitosan-coated poly(lactic-glycolic acid) (PLGA) nanoparticle involving the eukaryotic expression plasmid DNA of the Newcastle disease virus (NDV) F gene (pVAX I-optiF). This nanoparticle can control the release of plasmid DNA and activate stronger cellular, mucosal, and humoral immune responses than the naked plasmid DNA vaccine alone. Their results indicated chitosan-coated PLGA nanoparticles to be an effective and safe mucosal immune delivery system for the NDV DNA vaccine [187].

Recent reports discussed the fabrication of hepatitis B surface antigen with chitosan−polyethylene glycol nanocomposite (HBsAg−CS−PEG NC) via in situ ionic gelation method, which forms a highly stable nanoformulation. The developed nanocomposite exhibits high antigen loading capacity and entrapment efficiency. In vitro release profile showed a gradual increase in release at increasing time intervals, thus indicating stable release. The increased immunogenicity of the nanocomposite was estimated by rosette formation, induction, and phagocytosis rate using T cell rosette formation assay (TCRF assay) and mouse monocyte macrophage phagocytosis assay. No sign of toxicity was observed in the Wistar rat model. Hemocompatibility analysis demonstrated that nanocomposite treatment did not show hemolysis, changes in antioxidative enzymes, and serum protein profiling, which confirms the biocompatibility of nanocomposite. Their overall findings reflected that HBsAg vaccine nanoformulation can be utilized as a successful immunizing agent [188].

5.7 Fluorescent polymeric nanovehicles

The goal of developing fluorescent polymeric nanoparticles as a delivery vehicle is to trace delivery pathways through a fluorescent microscope and understand the morphology of nanoparticles, which affect the suitability for drug delivery applications.

Published literature has reported the synthesis and characterization of two different classes of polymeric nanoparticles: *N*-isopropyl acrylamide−based thermoresponsive nanogels and copolymer P(TEGA)-b-P(d, lLA) nanomicelles. They covalently attach nanoparticles to fluorescent tags and demonstrate their ability to internalize and monitor postnatal subventricular neural stem cells up to 150 μg/mL without disrupting their proliferation, multipotency, and differentiation characteristics. The difference in the chemical structure of nanogels and nanomicelles does not affect their toxicity but affects their loading capacity. When retinoic acid is loaded into nanogels, it improves the drug solubility in aqueous solutions and shows a clear pharmacological effect with increased production of neurons as a result of the modulation of neural subventricular zone stem cells [189].

5.8 Fluorescent bioimaging

Fluorescence imaging is used for successful drug release at the tumor site. The dye-loaded nanoparticles are mainly used for in vitro and in vivo imaging. Qin et al. used fluorescent zeolitic imidazolate framework-8 nanoparticles loaded with doxorubicin (FZIF-8/DOX) as the core and a molecularly imprinted polymer (MIP) as the shell to synthesize tumor-sensitive biodegradable FZIF-8/DOX-MIP nanoparticles. The ability of synthesized nanoparticles to target fluorescence imaging and successful drug release has been demonstrated both in vitro and in vivo. Studies have shown that FZIF-8/DOX-MIPs

function as a diagnostic agent due to their successful targeting of MCF-7 cells and their stronger red fluorescence of embedded carbon quantum dots. Due to active targeting ability, good biocompatibility, tumor-sensitive biodegradability, and efficient drug release function, FZIF-8/DOX-MIPs can be extensively used in tumor imaging and treatment [190].

An easy strategy based on a solid-phase transformation of the template into polymer-coated carbonaceous nanodots (pCNDs) was used to synthesize multifunctional mesoporous silica nanospheres (MFMSNs) incorporated with dispersed fluorescent carbon nanodots. These homogeneous pCNDs were embedded into mesoporous silica nanospheres (MSNs) that act as the nontoxic fluorescence probe, resulting in highly efficient fluorescence imaging and anchoring sites for anticancer drug loading. There is a unique hydrophobic π−π/electrostatic interaction between pCNDs, aromatic drug molecules, and MFMSNs can also act as an advanced drug carrier for pH-triggered drug release [191].

Indocyanine green (ICG) is an FDA-approved near-infrared (NIR) imaging agent used primarily in the treatment of cancer. Jian et al. developed ICG-encapsulated hybrid polymeric nanomicelles (PNMs) by coassociating amphiphilic diblock copolymer poly(lactic-co-glycolic acid)−b-poly(ethylene glycol) (PLGA−b-PEG) and hydrophobic electrostatic complexes made up of ICG molecules and branched PEI. Results of in vitro cell uptake and cytotoxicity studies showed that this polymeric nanomicelle facilitates cell uptake of ICG by HeLa cells due to their near-neutral surface and thus enhances the NIR-triggered hyperthermia effect in the destruction of cancer cells. These reports indicated that ICG/PEI-loaded PNMs hold immense potential in cancer imaging and photothermal therapy [192].

5.9 Stem cell imaging

Stem cell imaging gives excellent knowledge on the nature and function of stem cells, particularly their position, protein expression rates, viability and percent viability, and differentiation status, as well as the interaction between cells and adjacent tissue.

Lamster et al. demonstrated that gadolinium-loaded synthetic melanin nanoparticles (Gd (III)-SMNPs) enhanced photoacoustic signal intensity up to 40-folds as compared with only synthetic melanin. This property makes these materials useful as dual-labeling agents as Gd(III)-SMNPs also behave as magnetic resonance imaging (MRI) contrast agents. These nanoparticles are used to label human mesenchymal stem cells. The stem cells−labeled Gd(III)-SMNPs were injected intramyocardially into mice, and photoacoustic and MR imaging of the tissue was observed. The result showed an improvement in the photoacoustic signal used in the in vivo image of the stem cells linking this modality to the MRI [193].

6. Future perspective

Polymeric nanomaterials have emerged as highly adaptable biomaterials with the potential to revolutionize a wide range of biomedical fields. The most significant advantage of polymeric nanomaterials is their synthetic versatility, as demonstrated by various synthetic procedures, which allows for precise control of size, shape, surface properties, geometry, composition, stability, degradation rates, and mechanical strength. These factors have been shown to play a key role in predicting the biological outcome of nanoparticle therapy, which has improved our knowledge of biological interactions with polymeric nanomaterials and is a foundation for developing better nanomaterials. Numerous preclinical studies indicate that polymer nanomaterials have the potential to revolutionize drug delivery by modifying the pharmacokinetic and pharmacodynamic profile at active ingredients, thus improving therapeutic efficacy while lowering systemic toxicity. Although many nanoparticle formulations have been reported in preclinical studies in animal models, only a few have made it into clinical trials. The challenges that need to be overcome to accelerate the transition of nanomaterials from bench side to bed side include (1) the biocompatibility and biodegradability of polymers, (2) optimization of nanoparticle surface chemistries to achieve longer circulation times, desired biodistribution profiles, and tunable drug release kinetics, (3) development of easy and reproducible synthetic procedures or bioconjugation techniques for the attachment of active ingredients, (4) development of highly stable formulations with increased shelf life, (5) development of better chemical and biological characterization techniques to avoid the discrepancies arising from batch to batch variations, and (6) optimization of process chemistry parameters to develop easily scalable procedures.

The research on polymeric scaffold design focuses on the development of materials that act as biologically active support systems to restore, replace, or enhance tissue or whole-organ function. These scaffolds are designed to perform a variety of functions, including promoting cell−cell and cell−ECM interactions, permitting transfer of biological factors to enable cell survival, signaling, and differentiation, degrading into biocompatible components at a rate that corresponds to tissue regeneration and exhibits no toxicity in vivo. Several fabrication technologies have been developed to design scaffolds with the desired structural, mechanical, and porosity properties. Despite advances in scaffold design and fabrication, there are still many limitations, such as biocompatibility, surface topology, and mechanical properties, which must be overcome to fabricate implants with the best performance.

7. Conclusion

Polymeric nanomaterials and nanocomposites have extremely appealing features that make them very attractive and amenable to a large number of versatile applications. This has led

to significant research focus on their design, development, and synthesis that have evolved and expanded the landscape of their applications across diverse sectors with pharmaceutical and healthcare industries being a very important end user. The polymer-based nanocomposites are used as a carrier for sustained drug delivery, polymer-based implants are used to repair bone and soft tissue, and dental implants prevent microbial growth and biofilm formation. Recent reports indicate their application in 3D printing and tissue regeneration. Major progress has been made in the design of polymer-based bionanocomposites due to the unique characteristics of nanosized reinforced structures. The formulation and surface modification of nanofillers open up new opportunities to investigate its utility in the development of polymer-based bionanocomposites for biomedical applications. These polymeric bionanocomposites display significant improvement in physicochemical and biological properties compared with virgin polymer and therefore provide a new approach in drug delivery, stem cell imaging, and tissue engineering.

This chapter presents a comprehensive review of biomedical applications of polymer bionanocomposites encompassing simple to more complex uses ranging from cell growth scaffolds to biosensors. Despite the good amount of research being done on the development of polymer-based bionanocomposites, many drawbacks need to be addressed. Before the use of bionanocomposites as nanomaterials, attributes, such as biocompatibility, biodegradability, and other supporting variables, need to be properly assessed in preclinical studies. The materials need to be carefully selected while designing nanocomposites and their cellular interactions be systematically investigated so that they can be used appropriately and translated effectively into biomedical applications.

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CHAPTER 7

Photocatalytic metal bionanocomposites for biomedical applications

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1. Introduction

The nanoscale field had gained the attention of the scientific community by the synthesis of nanomaterial with high optical, mechanical, chemical, and biological properties [1,2]. This nanosized dimension creates an improvement of different properties of nanocomposites compared with the conventional one where nanocomposites are a combination of organic and inorganic materials [3], whereas the interaction between organic and inorganic materials is strong by a covalent bond and/or is weak by interaction bond that affects the interface and the inner interface of the formed nanocomposites [4]. Next to various applications of nanocomposites in packaging, aerospace, automotive, and biotechnological industries, their synthesis via prepolymerization and postpolymerization methods has toxic effects that restricted their use [5,6]. For this purpose, scientists have examined the formation of new biohybrid materials named bionanocomposites due to their biocompatibility, biodegradability, and multiple functionalities [7].

Bionanocomposites are presenting an important class of nanomaterials consisting of the assembly of a natural matrix reinforced with organic or inorganic fillers on a nanosized dimension range [8]. The matrix is a continuous phase formed of polymer, metal, or ceramic. The biodegradable polymer can be derived from different natures such as biosources (cellulose, starch, and chitin), biosynthesized by microorganisms (polyhydroxybutyrate and polyhydroxyvalerate), petroleum sources (poly[(butylene succinate)-co-adipate] and poly [butylene adipate-coterephthalate]), and renewable sources such as poly(lactic acid) (PLA) [7,8], while various types of nanofillers have been combined with the biodegradable polymer matrix to form the bionanocomposites, such as graphene, silica, carbon nanotube, clays, hydroxyapatite, organic compounds, and metals [8,9]. Considering the different properties of

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bionanocomposites, this chapter aims to highlight the use of metals and metal oxides such as TiO_2, Ag, Au, ZnO, and Cu as a base of bionanocomposites.

Metals are mineral bodies with excellent electrical and thermal properties. They are represented in 91 metallic elements dispersed in nature under metallic and nonmetallic forms. The reaction between metal and oxygen will lead to the formation of metal oxides, such as MgO and TiO_2. Thanks to nanotechnology applications, they are applied in tremendous nanomaterials-based metal to develop novel devices [10]. Furthermore, metal-based bionanocomposites (MBNCPs) have shown widespread use in bionanocomposites areas due to their small size, quantum dimensions, and large active surface area [11]. Their synthesis is generally established by different methods, such as sol−gel, hydrothermal, melt deposition, ultrasonic, and nonhydrolytic approaches [12]. The use of metal gives potential strength, stiffness, and ductility to bionanocomposites. Besides, they enhanced their optical, magnetic, mechanical, thermal, electrical, and physicochemical properties [13]. Moreover, the photocatalytic properties of the MBNCPs have attracted much interest in different fields. The photocatalyst can use light energy (visible or UV light) to carry out oxidation and reduction reactions [14]. The photoexcitation generates reactive oxygen species (ROS), which induce mortality of the cells and decomposition of organic compounds. Thus, MBNCPs are applied in many areas including wastewater treatment, microorganisms inhibition, solar cells, packaging industries, fuel cells, biomedical, and biosensing applications [11,15,16].

In the biomedical sciences, the use of conventional biomedical materials has revealed major problems associated with the failure of medical devices. As the demand grows, the necessity to develop a nanoscale material offering high quality, safety, and functionality is required [17]. The development of biomimetic materials that can be used in biological and medical fields is highly challenging in nature. Thereby, the use of photocatalytic MBNCPs presents a promising route due to their biocompatibility, biodegradability, nontoxic, stability, and catalytic features [13].

MBNCPs have attributed an important capability to function with the human body and generate potent clinical therapy without undesirable effects. They play a crucial role in controlled drug delivery by enhancing the stability and the bioavailability of the drug, targeting cells, and offering the slower and constant release of the drug [18]. There are several drug delivery systems based on photocatalytic MBNCPs, which can deliver antitumoral drugs, antiinfection drugs of urinary and genital tracts, prostatitis, and eye infection and antiepilepsy drugs (Othman [19]). The incorporation of the drug into the MBNCPs alleviates their side effects and improves their therapeutic effects. They have also revolutionized gene therapy by developing gene nanocarriers with high transfection efficiency [13]. This therapy can prevent or treat the genetic disorder by loading single-stranded DNA or RNA on the MBNCPs, which give the protection from cleavage enzymes and deliver them to the target site [6,20].

The tissue engineering and wound healing fields have also found a place in the applications of MBNCPs. They formed an ideal scaffold for tissue engineering that promoted cell adhesion, proliferation, differentiation, and migration [21]. The nanofillers of MBNCPs demonstrated an excellent ability to carbonate and calcium phosphate and nourish osteoclasts and osteoblast bone cells [22]. Furthermore, the photobiocidal activity of MBNCPs makes them very promising in wound tissue healing, which can act as a dressing material for wound treatment and preventing wound infections [23]. Moreover, MBNCPs can serve as effective biosensor materials for different biological elements, such as glucose, H_2O_2, and carbohydrates, as well as for cancer detection [24]. The MBNCPs exhibit a fast detection with high sensitivity, good reproducibility, and precise response. The use of MBNCPs as screening and bioimaging devices showed for rapid and real-time detection of molecular biomarkers of dysfunctional cells and diseases. Thus, this chapter reports recent progress in bionanocomposites as well as the implication of metals as enhancing agents with high photocatalytic properties. In addition, it presents crucial applications of MBNCPs in biomedical fields.

2. Overview of bionanocomposites

Bionanocomposites are an emerging class of nanosized materials composed of an assembly between biodegradable matrix and inorganic or organic natural nanofillers such as metal, metal oxide, carbon-based nanomaterials, and silica [21]. They are promising alternatives to nanocomposites with harmful impacts on the environment due to their toxicity and synthesis limitations, while bionanocomposites demonstrate a nontoxic material with high performance, biocompatibility, biodegradability, and functional properties [7]. The synthesis of uniform bionanocomposites is frequently based on several techniques such as in situ polymerization, solution casting, melt processing, electrospinning, and processing under supercritical conditions [8]. The choice of synthetic method depends on the type of material and desired characteristics of the bionanocomposites (size, shape, and crystalline form) [12]. The melting or green synthesis approach is the most used method for the synthesis of bionanocomposites due to the absence of solvent and high incorporation of nanoparticles within the polymer in the molten state [8]. During the green process, the dispersion of different nanofillers within the matrix required two main factors, which include enthalpic interaction between the biopolymer—nanoparticle and optimizing processing conditions [25]. In the case of in situ polymerization and solution casting processes, the possible persistence or adsorption of the liquid monomer or/and organic solvents on the surface of bionanocomposites can cause certain drawbacks in medical applications [1,7,26], while electrospinning processing under supercritical conditions has gained vital interest due to the good dispersion of bionanocomposites giving excellent mechanical properties [27]. Three different types of

nanofiller dispersion within bionanocomposites are identified: (1) particulate bionanocomposites, (2) elongated particle bionanocomposites, and (3) layered structure bionanocomposites [7].

Different classes of bionanocomposites can be structured based on the nature of the matrix, the nanofiller, the size, and the shape Fig. 7.1 [27]. The nature of the biopolymer presents a wide range of components such as cellulose, chitosan, PLA, starch, chitin, polyhydroxyalkanoates, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), and some

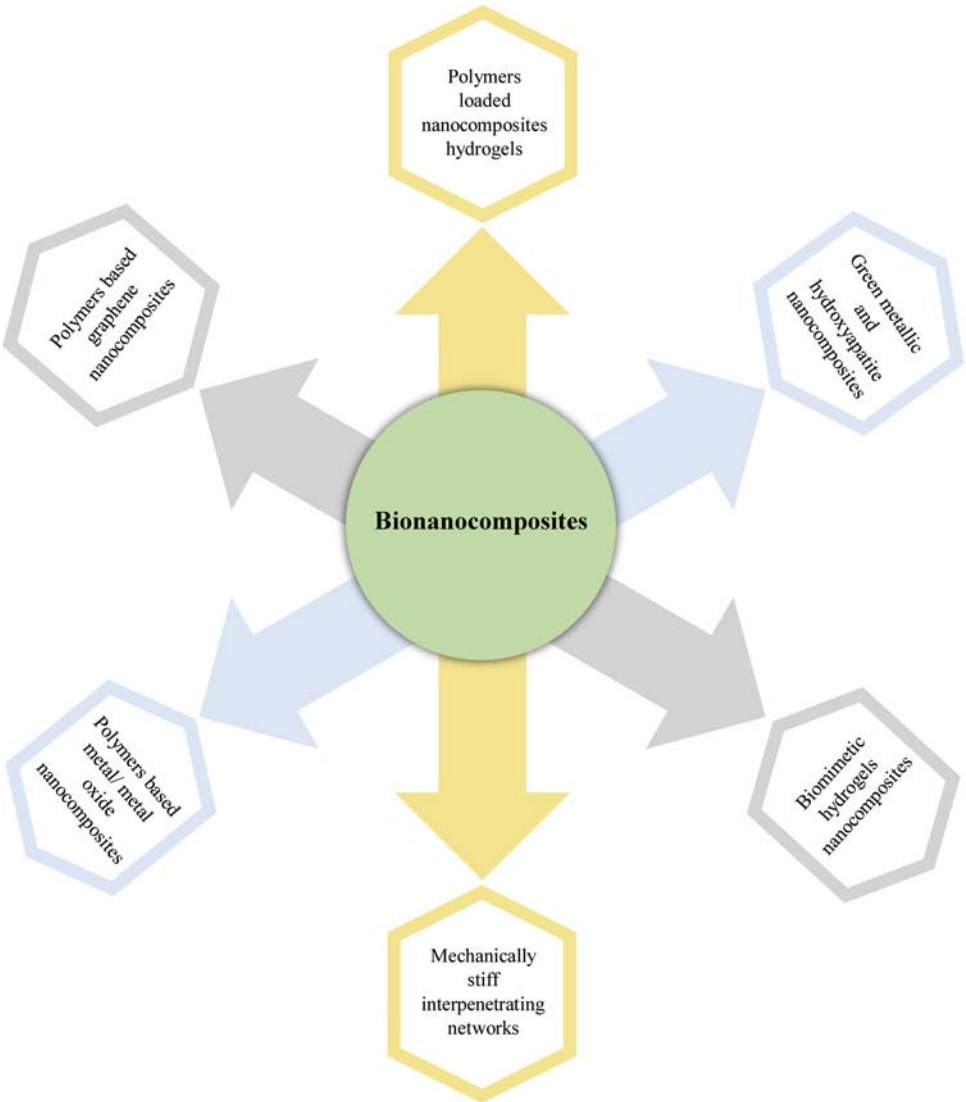

Figure 7.1
Classes of bionanocomposites.

other water-soluble biopolymers [13]. However, the sensibility and the instability of biopolymers need some modifications to improve their properties. For this purpose, the perfect improvement has been found in the combination of nanofillers or nanoparticles with the biopolymer, which confers more mechanical properties and potential barriers [19]. Generally, the type of incorporated nanofillers differs from organic to inorganic materials and extremely affects the type of bionanocomposites. Silica-based bionanocomposites have been highly used in musculoskeletal tissue engineering applications due to their bioadsorbent, advanced thermal, and surface stability [28]. Also, the characteristics of graphene oxide, which can disperse and stabilize the bionanocomposites, attracted considerable attention in tissue engineering and gene delivery [29].

Metal and metal oxide nanoparticles (M/MONs) are widely used as nanofillers due to their large surface area and volume ratio, high surface energies, and potential surface plasma resonance properties [2]. While many metal nanoparticles have found their way to synthesize through green methods with maintaining properties same as chemical methods, the use of M/MONs becomes very promising in the bionanocomposites area [13]. The inclusion of M/MONs into the matrix provides various enhanced functionalities of bionanocomposites [10,27] as listed in the following:

(i) improves rigidity, good affinity, and stability;
(ii) gives electrical, electrochemical, catalytic, and photocatalytic properties;
(iii) enhances thermal and mechanical properties; and
(iv) carries high functional surface area with potential biological activities.

Consequently, the M/MON bionanocomposites open up new potential to create innovative bionanocomposites with highly needed properties, which can replace the conventional bionanocomposites in a wide variety of applications.

3. Photocatalytic activity of metal bionanocomposites

The photocatalytic activity is intimately associated with the particle size of nanomaterials. Photocatalysis nanomaterials have been attracting much interest due to their specific acceleration of the conversion of light energy to oxidation and reduction processes (Fig. 7.2). Generally, MBNCPs exhibit more photocatalytic properties compared with conventional nanomaterials. In addition, they represented high stability, availability, nonphotocorrosive, and environmentally friendly [30].

3.1 TiO_2 bionanocomposites

Among various photocatalytic MBNCPs, TiO_2 is one of the most commonly used photocatalysts. TiO_2 showed efficient photoactivity, fast recombination of the

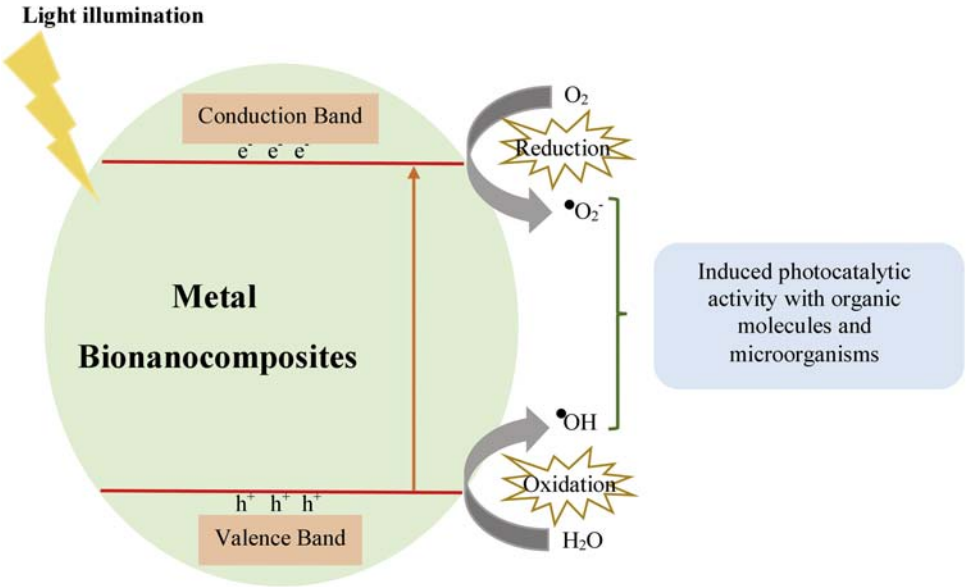

Figure 7.2
Schematic representation of the photocatalytic action of metal bionanocomposites.

photogeneration, nontoxicity, high stability, and a wide array of applications. The TiO_2-based bionanocomposites can be synthesized by different methods such as ultrasonication and sol–gel methods as shown in Table 7.1. However, the photocatalytic efficiency of TiO_2 strongly depends on the associate carbon materials, which increase the number of active sites [38]. Cai et al. [32] proved that resin-based TiO_2 bionanocomposites enhanced photocatalytic activity even after cessation of UV irradiation, as well as the photobactericidal activity. Likewise, the use of chitosan combined with TiO_2 attracted considerable attention as a stabilizer and an enhancer of photocatalytic activity [35]. Recently, Rehim et al. [53] developed a photocatalytic paper sheet, composed of TiO_2 associated with sodium alginate bionanocomposites with an excellent photobiocidal activity. Additionally, TiO_2-based graphene bionanocomposites revealed an effective associate material with high thermal and optical properties where the graphene material played a role of the acceptor and the transporter of electrons photogenerated during TiO_2 excitation [54]. The photoexcitation of TiO_2 generates the formation of ROS leading to demolish the cell membrane of microorganisms, alterations of the coenzyme A-dependent enzyme activity, and DNA damage [55] (Fig. 7.3).

3.2 Mixed metal oxide bionanocomposites

It was well established that the combination of one or greener metals enhances the photocatalytic properties of MBNCPs. Abdulla-Al-Mamun et al. [15] synthesized

Table 7.1: Photocatalytic properties of metal bionanocomposites.

Metal bionanocomposites	Methods	Applications	References
Cu:TiO_2—chitosan bionanocomposite	Sol—gel and ultrasonication	Photocatalytic—antimicrobial activity under visible light	[31]
TiO_2/resin bio-nanocomposites	Sol—gel	Implant coatings Photobactericidal activity under and after UV light	[32]
TiO_2/poly[2-(tert-butylamino) ethyl methacrylate co-ethylene glycol dimethacrylate] bionanocomposites	Surface-initiated photopolymerization	Photobactericidal activity under UV light	[33]
TiO_2/biocidal polymer anatase bionanocomposites	Sol—gel	Antimicrobial coating Photobiocidal activity under UV light	[34]
TiO_2/chitosan bionanocomposites	Hydrothermal	Photocatalytic degradation of malachite green	[35]
NiO/PVA-MF	Ex situ	Photocatalytic—antimicrobial activity	[36]
TiO_2/PLGA [poly(lactic-co-glycolic acid)] bionanocomposites	Sol—gel	Photobiocidal activity Biomedical dressing	[37]
TiO_2/graphene bionanocomposites	Sol—gel	Photocatalytic—antimicrobial activity	[38]
TiO_2—ZnO bionanocomposites	Nonhydrolytic	Photocatalytic—antimicrobial activity under UV light	[39]
TiO_2—Ag nanocomposite-based microheterogeneous Ag@ Fe-doped TiO_2 bionanocomposites	One-step solvothermal	The photocatalytic inhibition of cancer cells	[15,40]
Ag-embedded ZnO bionanocomposites	Facile and single-step soft chemical	Photodynamic therapy	[41]
Fe_3O_4—ZnO bionanocomposites	Facile two-step strategy	Photocatalytic degradation of methyl orange Drug delivery and diagnostics	[42]
FeS_2—Bi_2O_3 bionanocomposites	Ultrasonic	Photocatalytic—drug delivery systems	[43]
Au—TiO_2 bionanocomposites	Controlled hydrolysis	Photodegradation of methanol to formaldehyde	[44]
Mg—TiO_2 bionanocomposites	Melt deposition	Photocatalytic biomedical applications	[45]
$BiVO_4$/$Bi_2O_2CO_3$ bionanocomposites	Hydrothermal	Photocatalytic biomedical engineering	[46]
ZnO/bacterial modified cellulose bionanocomposites	Green synthesis	Photocatalytic wound dressing	[23]

Continued

Table 7.1: Photocatalytic properties of metal bionanocomposites.—cont'd

Metal bionanocomposites	Methods	Applications	References
ZnO/Ag-genipin-cross-linked chitosan/poly(ethylene glycol)/bionanocomposites	Sol—cast transformation	Photobiocidal activity Wound dressing	[47]
ZnO—Ag/poly(vinyl alcohol)/chitosan/cellulose nanocrystal bionanocomposites	Solution casting	Photocatalytic—antimicrobial activity under UV light	[48]
MgO/graphene bionanocomposites	Sonication-assisted solvothermal	Photocatalytic—antimicrobial activity	[49]
Y_2O_3/graphene oxide bionanocomposites	Low-temperature solution	Photobiocidal activity	[50]
CeO_2/g-C_3N_4 bionanocomposites	Hard template	Photocatalytic—antimicrobial activity under solar light	[51,52]

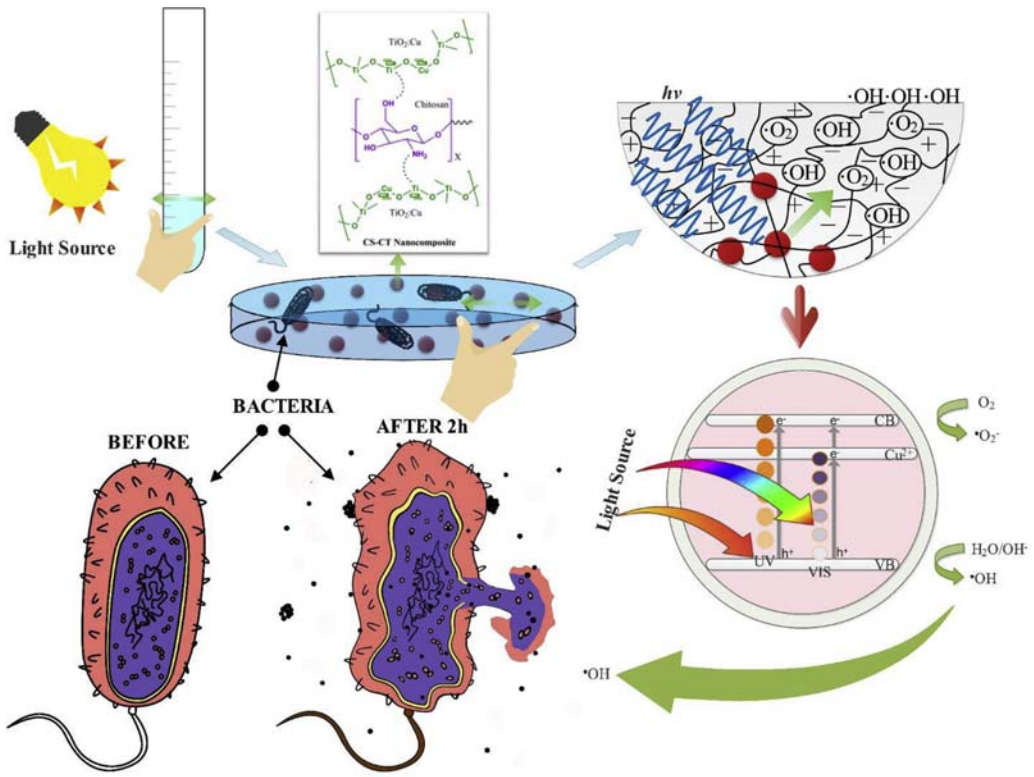

Figure 7.3

Mechanism of photocatalytic chitosan-TiO_2: Cu bionanocomposites on microbial cells. *Copyright 2016, Elsevier B.V. From A.V. Raut, H.M. Yadav, A. Gnanamani, S. Pushpavanam, H. Pawar, Synthesis and characterization of chitosan-TiO2 :Cu nanocomposite and their enhanced antimicrobial activity with visible light, Colloids Surf., B 148 (2016) 566—575.*

bionanocomposites based on Ag@ Fe-doped TiO_2 by the sol–gel method. The photocatalytic activity was evaluated through the photocatalytic killing of cancer cells under visible light, and it showed a higher catalytic cancer inhibition than conventional Ag, Fe, or TiO_2 nanocomposites [15,40]. Likewise, the green synthesis of Ag associated with ZnO bionanocomposites proved a higher photocatalytic and photobiocidal activity, which produce an abundant amount of ROS [41]. Similarly, Karthik et al. [56] developed a multifunctional CdO–NiO–ZnO mixed metal oxide bionanocomposite that has an excellent photobiocidal activity. Several other mixed metal oxide bionanocomposites, such as TiO_2–ZnO, FeS_2–Bi_2O_3, Au–TiO_2, and Mg–TiO_2, as well as their applications have been summarized in Table 7.1 [39,42,46,44].

3.3 Polymer–metal and graphene metal bionanocomposites

The incorporation of MBNCPs inside the polymeric systems enhanced their stability and their multiple properties. Bhat et al. [36] showed that bionanocomposites based on NiO/PVA-MF (melamine formaldehyde) have uniform, smooth, free-standing, hydrophobic, and stability features with high photocatalytic activity. The integration of NiO increases the photobiocidal activity against various bacteria as well as the biodegradation of dye color. Moreover, Guin et al. [57] demonstrated photoreduction and photobiocidal activities under UV light of bionanocomposite silver combined with PVA synthesized by a green synthesis method. On the other hand, chitosan-coated zinc oxide bionanocomposites obtained by a green method using bioflavonoid rutin demonstrated a potential photocatalytic activity under solar light [58]. Additionally, the green synthesis of iron oxide loaded in chitosan bionanocomposites revealed efficient photocatalytic properties in diverse biomedical applications such as antimicrobial and antioxidant activities [59]. Furthermore, Youssef et al. [60] prepared a hybrid of chitosan/polyethylene glycol (PEG)/calcium silicate loaded with ZnO bionanocomposites by using a sol–gel method that showed high optical, photocatalytic, and antimicrobial activities. Another study showed that the photocatalytic activity and biological applications of the nanocomposite were enhanced by reinforcing the hybrid chitosan/PEG with genipin after mixing them with ZnO and Ag bionanocomposites [47]. Recently, Sultana [61] developed polyaniline/chitosan-Ag bionanocomposites that are used as excellent materials for enhanced photodegradation, tissue engineering, drug delivery, and medical devices. The use of graphene in MBNCPs has shown excellent electrochemical and photocatalytic properties. Ravichandran et al. [62] revealed that Zn:Co loaded on graphene oxide bionanocomposites exhibit high photocatalytic and photobiocidal activities. Moreover, Wang et al. [63] have been successively synthesized graphene oxide combined with AgCl/Ag bionanocomposites with good visible light catalytic and potent elimination of biofilm and bacterial cells.

3.4 Other metal bionanocomposites

Due to their unique properties, carbon nanotubes (CNTs) have shown remarkable application in MBNCPs. Kamil et al. [64] fabricated CNT doped with TiO_2 by various methods with high photoelectrochemical activity. As well as, the hybrid of CNT with polyaniline loaded with silver bionanocomposites gave a potent photobiocidal activity against pathogenic microorganisms [65]. Furthermore, Theerthagiri et al. [51] synthesized multifunctional bionanocomposites hematite iron oxide (α-Fe_2O_3) combined with graphitic carbon nitride (g-C_3N_4) that showed an enhanced photocatalytic activity under visible light, which can be promising for nanodevices. Additionally, novel mesostructured CeO_2/g-C_3N_4 bionanocomposites have been developed with remarkable photocatalytic properties and antimicrobial activities under solar light [52].

4. Biomedical applications of photocatalytic metal bionanocomposites

Nowadays, MBNCPs attract a very large variety of functional biomaterials for biomedical applications, due to their biocompatible nature and catalytic properties [66]. For this purpose, different photocatalytic MBNCPs have been developed for the detection and treatment of diseases as shown in Fig. 7.4.

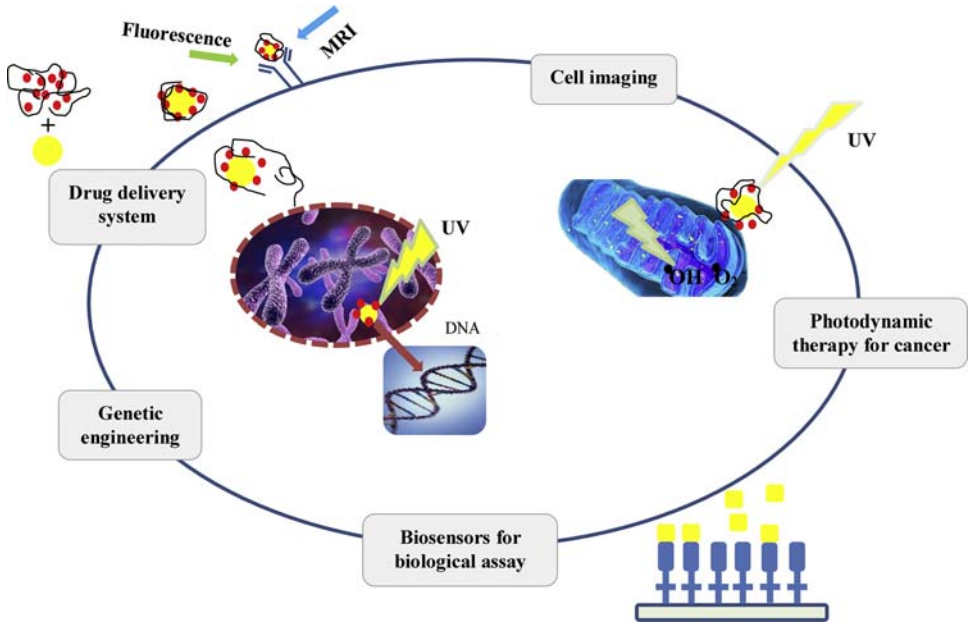

Figure 7.4
Schematic overview of the biomedical applications of photocatalytic metal bionanocomposites. *DNA*, deoxyribonucleic acid; *MRI*, magnetic resonance imaging; *UV*, ultraviolet.

4.1 Drug delivery

For decades, traditional drug delivery systems have suffered from uncontrolled drug delivery that is caused by the poor suitable concentration of the drug in the blood to a specific site, side effects, and the unsafety of other tissues [67]. The urgent need to develop new drugs with therapeutic effects is required. The use of nanotechnology allows the load and the carrier of a sufficient amount of drug on their large functional surface [18]. Drug delivery is consisting of the delivery of drugs to specific organs with a sufficient dose, pharmacokinetics, and optimal therapeutic effects. Thus, the nanotechnology is targeting on (1) avoiding the fluctuate of drug concentration while maintaining the constant dose and the specific target, (2) ultimate therapeutic effects with minimizing side effects and toxicity risks, and (3) efficiency, safety, and enhancing the drug delivery [18]. For this purpose, a novel drug delivery system based on MBNCPs was made as the new carrier to provide pharmaceutically active agents.

The synergy between organic material (example: biopolymers) and inorganic material such as noble metals (Ag, Ti, and Au)/metals (Zn and Fe) offers their potential use in MBNCPs for drug delivery [68] as displayed in Fig. 7.5.

The popularity of TiO_2 nanoparticles in bionanocomposites is due to their photocatalytic properties, low toxicity, excellent biocompatibility, and chemical stability [70]. Consequently, the use of photocatalytic TiO_2 nanocomposites in drug delivery generates reactive oxygen species under UV irradiation that sustained and destructed the tumor [71]. Generally, the use

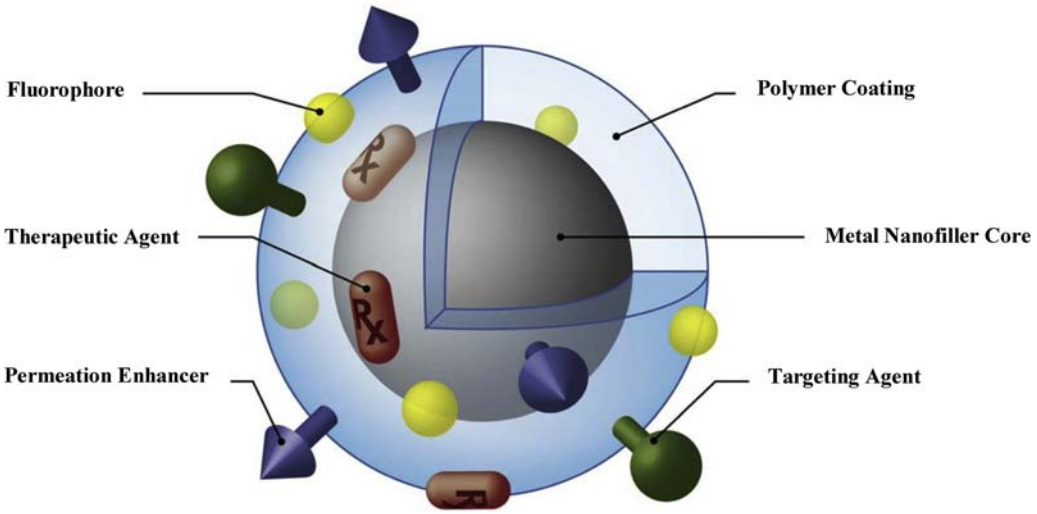

Figure 7.5
Structure of metal bionanocomposites in drug delivery. *Copyright 2008, Elsevier B.V. From C. Sun, J. Lee, M. Zhang, Magnetic nanoparticles in MR imaging and drug delivery, Adv. Drug Deliv. Rev. 60 (2008) 1252–1265.*

of nanochemotherapy to treat the abnormal cell proliferation is very promising where the cancer treatment can escape enzymatic degradation, renal filtration, and increasing the therapeutic effect. TiO_2 nanocomposites have been normally used as a nanocarrier of doxorubicin (DOX) in anticancer therapy. These bionanocomposites altered the biodistribution of the tumor, minimized the side effects of the drug, and generated ROS from TiO_2 under UV irradiation [72,73]. Also, Li et al. [74] and Wu et al. [75] revealed promising results of TiO_2 nanocomposites for cancer therapy. The fabricated nanocarrier (TiO_2 nanocomposites−daunorubicin) proved the antitumoral activity while alleviating the side effects of the daunorubicin drug. Furthermore, the high affinity of TiO_2 nanocomposites toward phosphate species makes it potentially useful for intracellular delivery of DNA oligonucleotides [75]. In another study, drug delivery of ruthenium complex based on TiO_2 bionanocomposites can generate ROS under visible light as well as UV light and induced mortality in melanoma cells [76]. In way to nanochemotherapy, a nanocarrier composed of TiO_2 nanocomposites and temozolomide, the main drug handling the brain tumor, was fabricated. The controlled new delivery of temozolomide showed an improvement in binding with DNA of cancerous cells, leading to their destruction. The high biocompatibility and the surface area also make TiO_2 nanocomposites a good candidate for valproic acid delivery, which is one of the most used drugs in epilepsy and bipolar disorder therapy. However, valproic acid is limited to the clinical application due to its low bioavailability and harmful side effects. Therefore, the development of new drug delivery formed of TiO_2−valproic acid improves the treatment of epilepsy and minimizes side effects of the drug [77].

Additionally, TiO_2-based bionanocomposites showed their efficiency in genetic engineering by nanocarrier of genes to resolve the genetic disorder. Fei [78] demonstrated the efficiency of the photocatalytic TiO_2 bionanocomposites to combine with DNA and transfer it to nuclei or mitochondria where it cleaves mutated genomic DNA and hybrids the new delivered DNA. Finally, the incorporation resulted in the photoactivation of TiO_2, which reveals the success of the therapeutic activity. Moreover, the addition of natural polymers such as chitosan, PLA, cellulose, and sodium hyaluronate to bionanocomposite resulted in powerful biomaterials with promising drug delivery systems. In a way to find better cancer therapy, a newly designed drug delivery was prepared of graphene oxide/TiO_2 nanoparticles/doxorubicin (GO/TiO_2/DOX) composites loaded on chitosan/PLA. This bionanocomposite enhanced the integration of DOX into cells, where the drug release is dependent on pH and the presence of a magnetic field that leads to high inhibition of lung cancer cell growth [79]. Likewise, Safaei et al. [80] synthesized sodium hyaluronate biopolymer−TiO_2 bionanocomposites with different ratio of biopolymer. The bionanocomplex demonstrated excellent anticancer activity against MCF-7 breast cancer cells.

The choice of nanocarrier for drug delivery is also a big challenge to treat urinary and genital tracts, prostatitis, and eye infections. Norfloxacin is one of the antibiotics treating these infections caused by different bacteria [81]. Its administration by the oral route

minimizes its bioavailability; for that, the use of nanocomposites based on biopolymer owing mucoadhesive property enhances its biodisponibility [82]. Interestingly, Salahuddin et al. [83] have fabricated MBNCPs formed of PLA and TiO_2 where norfloxacin was loaded on TiO_2 and encapsulated into the PLA. The new drug delivery system of norfloxacin showed high antibacterial and great antitumor activities. Likely, gold–iron oxide nanocomposites are also one of the most used nanocarriers in drug delivery applications in the treatment and monitoring of cancer [84]. Similarly, Ghorbani et al. [85] synthesized new bionanocomposites for the delivery of an anticancer drug named lipoic acid–curcumin based on gold–iron oxide nanocomposites and glutathione as the targeting ligand. The bionanocomplex demonstrated an excellent brain tumor therapy and promising candidate for tumor imaging, as well as alleviation of the side effects of the drug.

Sodium carboxymethyl cellulose (CMC) is a biopolymer that is widely used in drug carriers. Rasoulzadeh and Namazi [86] demonstrated a good performance of CMC/graphene oxide bionanocomposites in the delivery of DOX with efficient chemotherapy. The CMC/ZnO bionanocomposites proved high efficiency in drug delivery systems due to their biocompatibility [87]. The nanocarrier of propranolol hydrochloride drug by CMC/ZnO bionanocomposite was capable to enhance the bioavailability and the therapeutic effect of the drug. Moreover, the biocompatibility of new bionanocomposites based on CMC/ZnO nanoparticles/graphene oxide was examined in human blood cancer cells by delivering the DOX. The results revealed that the CMC/ZnO nanoparticles/graphene oxide enhanced the solubility, bioavailability, and controlled release of the drug [67].

A bionanocomplex chitosan/ZnO showed high potency as a nanocarrier for the ibuprofen drug, as shown in Fig. 7.6. The ibuprofen release depends on the swelling of hydrogel

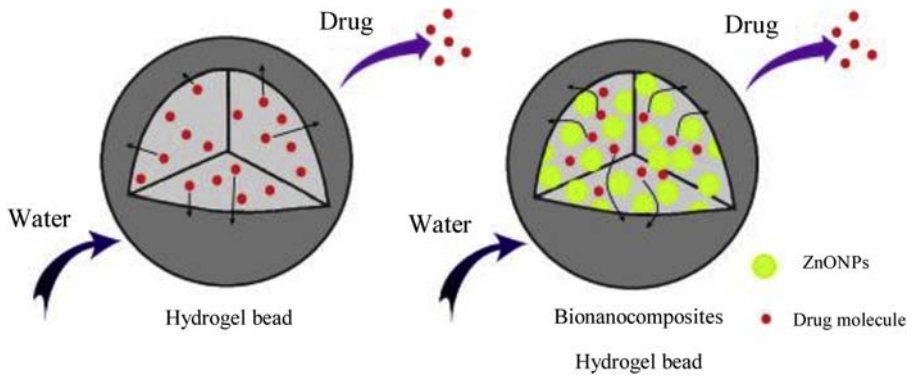

Figure 7.6

Mechanism of ibuprofen drug release from Zn-bionanocomposite hydrogel. *Copyright 2015, Elsevier B.V. From M. Yadollahi, S. Farhoudian, S. Barkhordari, I. Gholamali, H. Farhadnejad, H. Motasadizadeh, Facile synthesis of chitosan/ZnO bio-nanocomposite hydrogel beads as drug delivery systems, Int. J. Biol. Macromol. 82 (2016) 273–278.*

MBNCPs and the release time, which enhanced the controlled release of the drug and its therapeutic effects [88]. Venkatesan et al. [89] synthesized MBNCPs that consist of chitosan/hydroxyapatite by a coprecipitation method. The chitosan/hydroxyapatite-loaded celecoxib drug showed an excellent apoptotic death of colon cancer cells. It was also observed that the nanocarrier is highly biocompatible and hemocompatible with an efficient controlled release of modified or unmodified celecoxib. In another study, MBNCPs based on chitosan/Ag nanoparticles were designed and loaded with ibuprofen. The new drug carrier showed a great potential to control the release of the ibuprofen with a remarkable antibacterial property of the newly synthesized metal bionanocomposite [90].

4.2 Biosensor and bioimaging

Biosensor applications have high interest due to their sensitive electrochemical, simple fabrication, selectivity, and extensive uses in disease diagnosis. The affinity of biosensors typically relies on detecting specific biochemical reactions mediated by biological elements, such as an antibody, enzyme, and DNA. The use of conventional biosensors is limited on their low detection signal and restricted active surface area. Recently, several studies have been focused on the use of MBNCPs due to their enhanced biological and chemical detectability, stability, and environmentally friendly. Wei et al. [91] presented the first development of ZnO nanorods/Au hybrid bionanocomposites for sensitive and selective detection of glucose. The glucose biosensor was fabricated by entrapping glucose oxidase (GOx) in this composite matrix using a cross-linking method with glutaraldehyde and Nafion solutions. The MBNCP biosensor exhibited high and reproducible sensitivity, short response time, good storage stability, and high affinity to GOx. Furthermore, Wang and Zhang [92] developed graphene/nanogold/glassy carbon electrode bionanocomposites via the incorporation of GOx with graphene/nano-Au. It was found that the graphene/nanogold/glassy carbon electrode/GOx displayed an excellent sensitivity to glucose, good stability, and reproducibility. Furthermore, Hwa and Subramani [93] also synthesized glucose biosensors based on graphene/CNT/ZnO bionanocomposites by the one-pot method. This study revealed enhanced stability, repeatability, and reproducibility of the biosensor. On the other hand, Wayu et al. [94] fabricated a new biosensor for H_2O_2-structured CNT/ZnO bionanocomposites. These MBNCPs demonstrated high electrocatalytic activity and selectivity toward H_2O_2. Similarly, Thandavan et al. [95] prepared a biosensor for H_2O_2 based on CNT/Fe_3O_4 bionanocomposites. Results revealed high detection of H_2O_2 and quick response. In another study, Ali et al. [96] synthesized multiple novel metal bionanocomposites based on Pd nanoparticles/graphene oxide, Pt nanoparticles/graphene oxide, Ag nanoparticles/graphene oxide, and Au nanoparticles/graphene oxide for breast cancer diagnosis. These MBNCPs used the black pepper extract for the detection of epidermal growth factor receptor (ErbB2). Moreover, the linking of biomolecule TiNF with TiO_2 nanocomposites played an excellent role in the biosensor, as

well as in cell-capture assay for tumor cells detection [97]. Moreover, polymers have been used in biosensor applications, such as electronic devices, to enhance biosensor selectivity. The use of conjugated polymers coupled with gold nanoparticles had a high potential of detecting double-stranded DNA and enhanced fluorometric bioprobes for bioimaging applications [98].

Due to these enhanced properties of MBNCPs in biosensor applications, cell bioimaging found also a way to early detection of molecular biomarkers of dysfunctional cells and diseases. Certain MBNCPs have a fascinated function in cancer imaging due to their photocatalytic and electronic properties [99]. Lin et al. [100] synthesized MBNCPs based on iron oxide nanoparticles decorated with chitosan functionalized with polyethylene glycol and loaded with methotrexate and cyanine dye. As a result, the multifunctional of these MBNCPs revealed the efficiency of fluorescence and magnetic resonance bioimaging for cancer detection and therapy. Additionally, Ding et al. [101] prepared Fe_3O_4 nanoparticles with CdTe@ZnS quantum dots and CMC bionanocomposites that retain good fluorescence and magnetic properties in cancer cell imaging applications. While DOX was loaded on the MBNCPs giving an anticancer activity. Furthermore, Hadjipanayis et al. [102] presented a complex of magnetic nanoparticles and epidermal growth factor receptors as MBNCPs for targeted bioimaging of glioblastoma. Also, Ling et al. [103] developed a theragnostic polymer/superparamagnetic iron oxide bionanocomposites loaded with docetaxel drug that enhanced prostate cancer therapy and simultaneous ultrasensitive magnetic resonance bioimaging. Therefore, Wang et al. [104] used Fe@γ-Fe_2O_3@H−TiO_2 as core−shell metal nanocomposites for photothermal therapy, photothermal imaging, magnetic resonance imaging, and photoacoustic imaging, which showed promising aspects in cancer therapy as displayed in Fig. 7.7. The multifunctionalized metal−organic framework (Fe_3O_4@Bio-MOF) coated with folic acid−chitosan conjugate was successfully prepared for tumor-targeted delivery of curcumin and 5-fluorouracil. The MBNCPs are displayed as a smart theranostic agent, which improves magnetic resonance imaging resolution and visualization of cellular cancer [105].

4.3 Bone and cartilage tissues engineering

Designing biodegradable, biocompatible, osteointegration, and osteoinductor materials with high mechanical strength and antibacterial resistance are very required in the tissue engineering field as shown in Fig. 7.8. Biological methods aim the use of MBNCPs as an extracellular matrix for scaffold bone engineering due to their appropriate characteristics.

A new generation of silica polyhedral oligomeric silsesquioxane bionanocomposites has been used as promising cardiovascular tissue engineering with high cell viability and proliferation [107]. The results showed that the MBNCPs are suitable for the vascular prosthesis. Narayan [108] developed multiples diamond-like carbon—MBNCPs such as

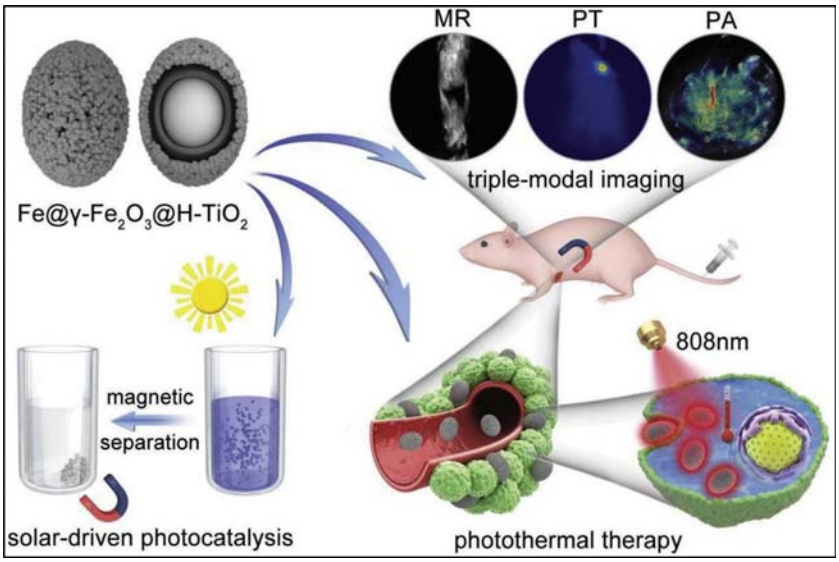

Figure 7.7

Applications of Fe@γ-Fe_2O_3@H−TiO_2 photocatalytic bionanocomposites in bioimaging and biosensors of cancer therapy. *Copyright 2018, Wiley-VCH. From M. Wang, K. Deng, W. Lü, X. Deng, K. Li, Y. Shi, B. Ding, Z. Cheng, B. Xing, G. Han, Z. Hou, J. Lin, Rational design of multifunctional Fe@γ-Fe2O3@H-TiO2 nanocomposites with enhanced magnetic and photoconversion effects for wide applications: from photocatalysis to imaging-guided photothermal cancer therapy, Adv. Mater. 30 (2018) 1706747.*

diamond-like carbon−copper, diamond-like carbon−silver, diamond-like carbon−silicon, and diamond-like carbon−titanium bionanocomposites, which exhibited excellent adhesion to medical prostheses surfaces and significantly smaller elastic modulus. In other studies, the use of bioceramic in bone tissue engineering scaffolds was very promising due to its osteoinductor property. Furthermore, Salarian et al. [109] synthesized bioceramic based on TiO_2 bionanocomposites, which revealed enhanced physical and mechanical properties of bone regeneration tissues.

Moreover, hydrogels are used to develop bionanocomposites for bone and cartilage tissue engineering. Zhang et al. [110] fabricated magnetic-based hydrogel bionanocomposites, which have a potential cartilage tissue engineering while responding to an external magnet. These MBNCPs could maintain the structural cartilage integrity and be used as a direct scaffold for the target cartilage site. In an attempt to find an ideal bone scaffold, an osteogenic scaffold based on strontium-substituted β-TCP and bioactive glass ceramics conducted rabbit bone marrow−derived mesenchymal stem cells. Results demonstrated that a porous structure of the MBNCPs presented efficient osteoinductive properties with inducing and accelerating the osteodifferentiation of mesenchymal stem cells [111].

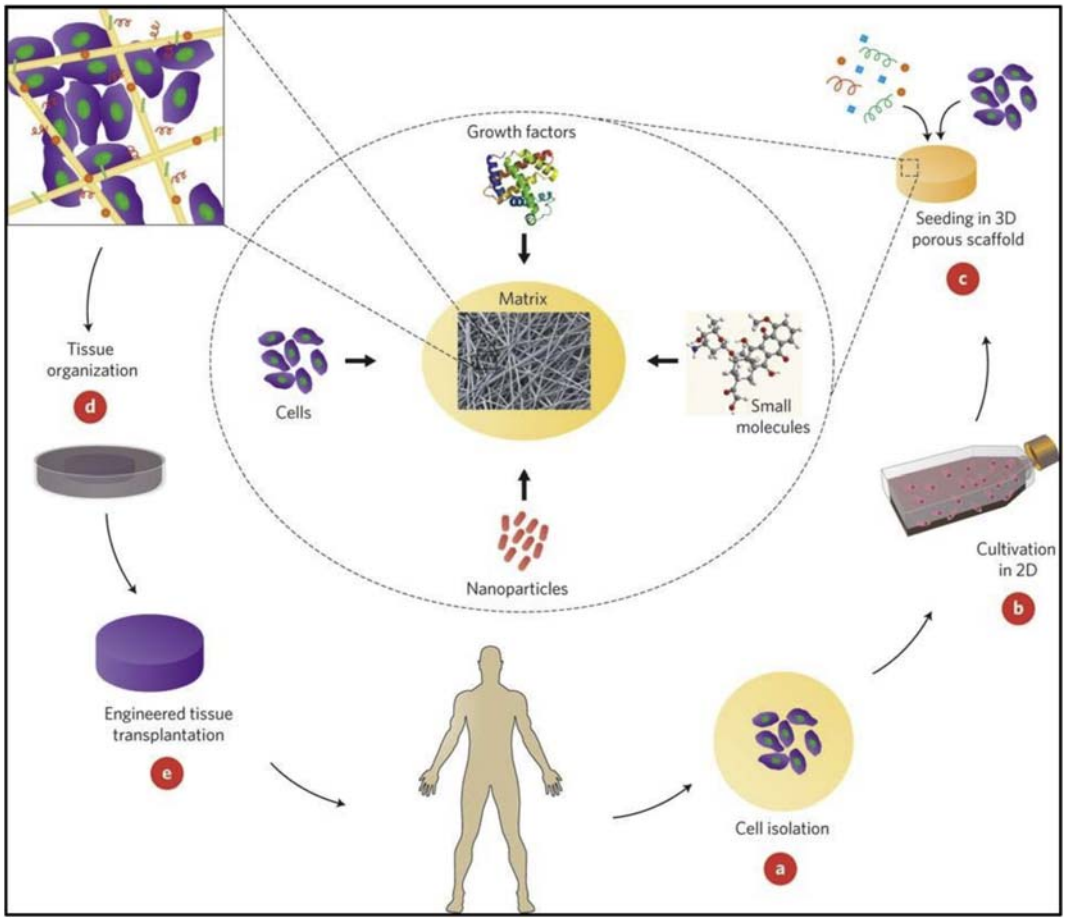

Figure 7.8

Bioactive scaffold for tissue engineering. *Copyright 2010, Springer Nature. From T. Dvir, B.P. Timko, D.S. Kohane, R. Langer, Nanotechnological strategies for engineering complex tissues, Nat. Nanotechnol. 6 (2010) 13–22.*

The incorporation of biopolymer in MBNCPs has played a vital role in articular cartilage tissue engineering. Cao et al. [112] designed biocompatible bipolymeric (PVA/PVP) hydrogel TiO_2 bionanocomposites to enhance osteoblast adhesions. The results showed that the MBNCPs significantly improved the bioactivity via lamellipodia and filopodia extension, the morphology, and the behavior of osteoblast cells as shown in Fig. 7.9A. Additionally, it demonstrated that high bactericidal activity made them a potential for articular cartilage tissue regeneration. Likewise, chitosan has received great attention in scaffold applications where Shaltooki [113] made a porous scaffold based on chitosan-coated by polycaprolactone/strontium substituted by bioactive glass bionanocomposites.

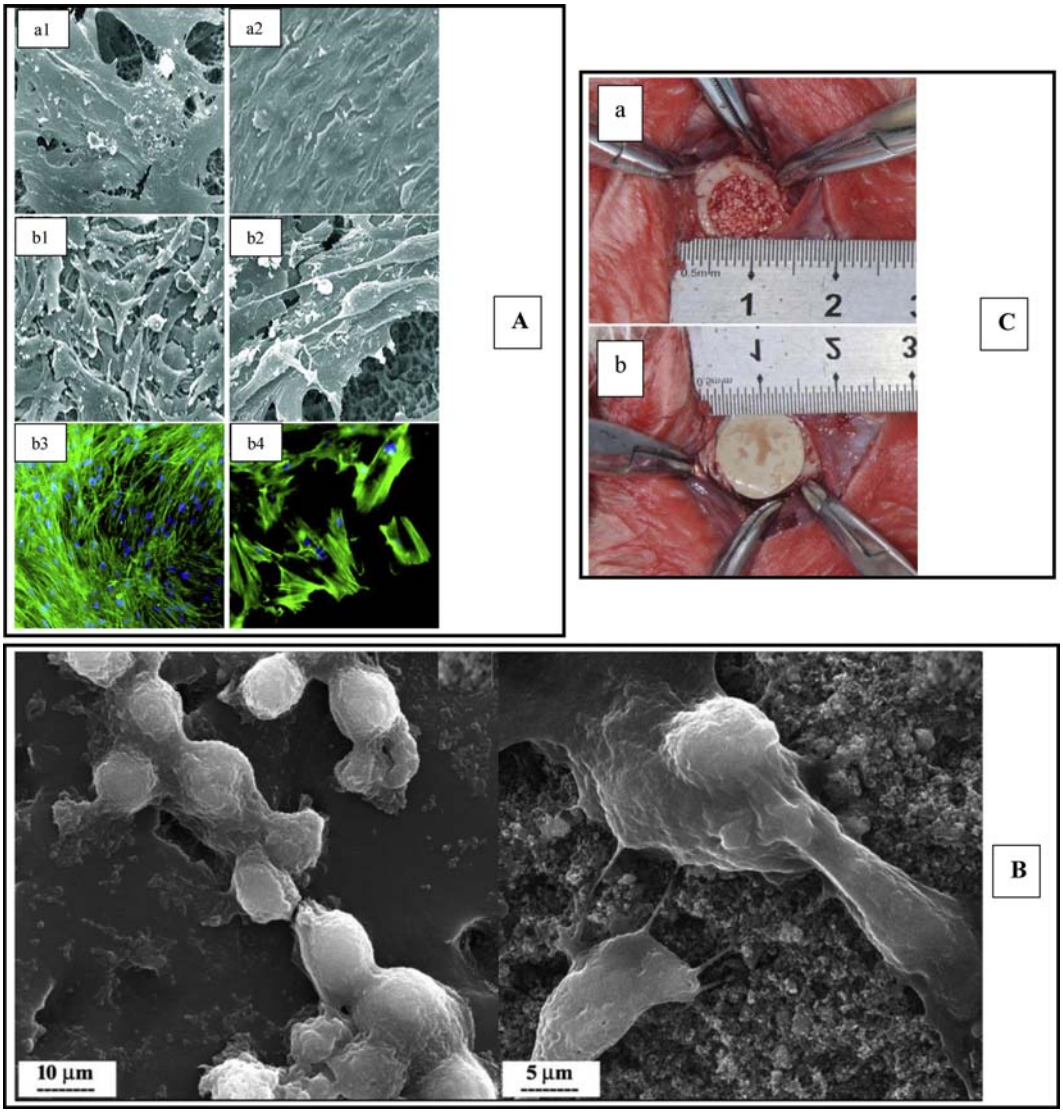

Figure 7.9

(A) (a1-a2) PVA/PVP and (b1-b2-b3-b4) PVA/PVP-TiO_2 bionanocomposites with HOS (MG-63) osteoblast cells. (B) SEM micrographs of the adhesion of MG-63 cells on the surface of chitosan coated by polycaprolactone/strontium substituted by bioactive glass bionanocomposite scaffold. (C) (a) Bone defects with a diameter of 8 mm were created on rabbit mandibles and then filled with deproteinized bovine bone granules. (b) Bone defects were covered with polarized $BaTiO_3$ poly(vinylidene fluoridetrifluoroethylene) nanocomposite membranes. *(A) Copyright 2018, Elsevier B.V. From L. Cao, X. Wu, Q. Wang, J. Wang J, Biocompatible nanocomposite of TiO2 incorporated bi-polymer for articular cartilage tissue regeneration: a facile material, J. Photochem. Photobiol., B 178 (2018) 440–446; (B) Copyright 2019, Elsevier B.V. From M. Shaltooki, G. Dini, M. Mehdikhani, Fabrication of chitosan-coated porous polycaprolactone/strontium-substituted bioactive glass nanocomposite scaffold for bone tissue engineering, Mater. Sci. Eng. C 105 (2019) 110138. (C) Copyright 2019, Dovepress. From Y. Bai, X. Dai, Y. Yin, J. Wang, X. Sun, W. Liang, Y. Li, X. Deng, X. Zhang, Biomimetic piezoelectric nanocomposite membranes synergistically enhance osteogenesis of deproteinized bovine bone grafts, Int. J. Nanomed. 14 (2019) 3015–3026.*

The MBNCPs have high bioactivity and cell attachment, which make them a good scaffold for bone tissue engineering as mentioned in Fig. 7.9B. On the other hand, a combination of natural biopolymers such as ß-tricalcium phosphate and collagen with strontium oxide nanoparticles has been synthesized by using a freeze-drying method [114]. The MBNCPs scaffold exhibited a high mechanical property and potential differentiation ability for the engineering of mesenchymal stem cells.

The insufficient treatment of bone defects by conventional bone graft with a barrier membrane required the development of alternative methods. The bone defect regeneration has been carried out by a flexible membrane formed of homogeneous distribution of piezoelectric $BaTiO_3$ nanoparticles embedded within poly(vinylidene fluoridetrifluoroethylene) matrix. These MBNCPs showed the highest osteoinductivity, potential bone repair, and regeneration ability, compared with conventional polytetrafluoroethylene membranes as shown in Fig. 7.9C [22].

4.4 Antimicrobial and antioxidant agents

Generally, biomedical devices suffer from microbial infection; thus, researchers considered designing biocompatible biomaterials with antimicrobial activity. Several studies investigated the use of MBNCPs due to their significant physicochemical and photocatalytic properties for disinfection. Thus, the MBNCPs based on TiO_2 nanoparticles are widely used in biomedical applications, mainly due to their high photobiocidal properties, which give an effective material against pathogenic microorganisms. Fu et al. [34] used anatase TiO_2 nanocomposites as a coating material because of their effective antibacterial activity. The developed antimicrobial materials based on biocidal polymer have been functionalized by TiO_2 bionanocomposites. The photobiocidal MBNCPs improved inhibition of bacterial growth under UV light and the antioxidant activity [33]. The enhanced antibacterial activity is more effective under UV light. In another study, Skorb et al. [115] fabricated a thin-film photocatalyst based on metal-modified TiO_2 and TiO_2:In_2O_3 nanocomposites. The MBNCPs film demonstrated high photobiocidal activity and photoproduction of both hydroxyl radicals and superoxide ions under UV light against pathogenic bacteria. The photobiocidal activity of the TiO_2 bionanocomposites is enhanced through a combination with graphene oxide matrix. The graphene oxide–based TiO_2 bionanocomposites showed high destruction of microbial cells by adhering to the cell surface, developing membrane stress, disturbing microbial interaction, oxidizing the cellular structure, and generating high amounts of ROS under solar light [38].

Among noble metals, silver is also known for its wide range of applications in health products such as wound healing, scaffold, and medical devices due to its strong antimicrobial activity. It has been reported that the silver-based cellulose

bionanocomposites are capable of causing bacteriostatic and bactericidal impacts more than silver ions and silver nanoparticles alone [116]. Furthermore, the carboxymethyl cellulose/silver bionanocomposites are enhanced by cross-linked layered double hydroxides. This hydrogel MBNCPs showed a potential antibacterial activity after silver incorporation with good stability of the bactericidal effect and effective antioxidant property [117]. Furthermore, Mallakpour et al. [118] have also developed biodegradable silver bionanocomposites containing poly(amide-benzimidazole-imide) with high antibacterial activity under solar light. Moreover, the use of biopolymer chitosan-based silver-organo-sepiolite bionanocomposites revealed a high antimicrobial impact against gram-negative and gram-positive bacteria [119]. Thus, photocatalytic silver-supported polyaniline/multiwalled CNT bionanocomposites designed by using in situ polymerization proved their effective antibacterial applications under UV light and their benefits in the biomedical field [65].

Furthermore, other MBNCPs are widely used as antimicrobial agents due to their biodegradability and environmentally friendly and are based on zinc, copper, and magnesium nanoparticles. The advantage of using these metals instead of noble metals is summarized in their lack of color and UV-blocking properties. The zinc-based carboxymethyl cellulose bionanocomposite hydrogel, zinc-based carboxymethyl chitosan bionanocomposite hydrogel, and zinc-based oxidized starch bionanocomposite hydrogel have been developed with the high swelling ability to various pH and excellent immunological and antibacterial properties against human pathogens [120,121,122], while the oxidative property of the zinc oxide nanoparticles was enhanced with a combination of chitosan and polypyrrole bionanocomposites [123]. Likewise, bionanocomposites-based magnesium nanoparticles are getting great interest from scientists because of their low cost of preparation [1]. Arshad et al. [49] synthesized multifunctional graphene nanoplatelets-based magnesium oxide bionanocomposites, which showed high photocatalytic and antimicrobial properties. In addition, Safaei et al. [124] enhanced the thermal resistance of cellulose-based magnesium oxide bionanocomposites, which demonstrated high stability and antibacterial properties that could be promising as a coating for medical devices. Therefore, copper-based materials also proved their good stability and renewability as antimicrobial agents as listed in Table 7.2. Likewise, Yadollahi et al. [137] designed bionanocomposite hydrogels formed of carboxymethyl cellulose and copper oxide nanocomposites with higher antibacterial activity. In recent studies, the use of chitosan matrix in MBNCPs enhanced their stability and their antibacterial properties. Antibacterial bionanocomposite hydrogels were prepared based on using copper oxide with a combination of chitosan or carboxymethyl chitosan. The hydrogels showed a high swelling capacity depending on the abundance of copper oxide nanoparticles with an excellent inhibition of microbial growth and antioxidant activity [138,139].

Table 7.2: Application of photocatalytic noble and titanium metal bionanocomposites in diverse biomedical applications.

Metal bio-nanocomposites	Method of preparation	Therapy	Applications	References
Gold-based graphene—three-dimensional nanostructure bionanocomposites	One-step electrochemical codeposition	Genetic engineering	Electrochemical DNA biosensor	[125]
Gold-based gelatin bionanocomposites	An ice particulate	Cancer therapy	Photothermal applications and implantable materials	[126]
Gold-based dextran bionanocomposites	Chemical reduction	Atherosclerosis detection	CT imaging agents	[127]
Silver/gold nanoparticles—based fibrin—gelatin bionanocomposites	Ex situ dispersing	Wound healing and antimicrobial activity	Hemostasis hastens wound healing	[128]
Silver-based bioceramic bionanocomposites	Sol—gel	Bone tissue regeneration Antimicrobial activity	Bone filling and reconstructive surgery applications	[129]
Silver-based poly(acrylamide)/poly(vinyl pyrrolidone) semi-IPN hydrogel bionanocomposites	In situ polymerization	Antimicrobial and antioxidant activities	Biomedical dressing	[130]
Silver-based poly-D, L-lactide-co-glycolide nanocomposites	Spreading	Wound healing and antimicrobial activity	Biomedical dressing	[131]
Silver-based agar bionanocomposites	Green	Antimicrobial and antioxidant activity	Biomedical dressing	[132]
TiO_2 bionanocomposites based on bioceramic device	Sol—gel	Inhibit the uncontrolled brain activity	Delivery of neurological drugs	[133]
TiO_2/chitosan bionanocomposites	Ultrasonic radiations	Cancer therapy	Drug delivery	[68]
TiO_2/tetra sulfonatophenyl porphyrin bionanocomposites	Ultrasonication	Photodynamic therapy of rheumatoid arthritis	Target cellular bioimaging and drug delivery	[134]
TiO_2/poly(ester urethane) urea bionanocomposites	Electrospinning	Bone tissue regeneration	Extracellular scaffold matrix-like fibrous	[135]

Continued

Table 7.2: Application of photocatalytic noble and titanium metal bionanocomposites in diverse biomedical applications.—cont'd

Metal bio-nanocomposites	Method of preparation	Therapy	Applications	References
TiO_2/sodium alginate bionanocomposites	Precipitation	Antibacterial and antifungal activities	Hygienic applications	[53]
TiO_2/modified with reduced graphene oxide bionanocomposites	Water spreading/ hydrothermal	Bone tissue regeneration Antimicrobial activity	Free-standing porous scaffolds	[78,136]
TiO_2/DNA nanocomposites	Electronically link by using bridging ligands	Gene therapy	Cleave mutated genomic DNA	[70]
Copper-based graphene bionanocomposites	In situ chemical reduction	Detecting carbohydrates	Biosensor	[24]
Copper oxide/ carboxymethyl cellulose hydrogel bionanocomposites	In situ oxidation	Antimicrobial activity	Biomedical dressing	[137]

4.5 Other biomedical applications

Wound care is a major difficulty because of the infection treatment that delays the healing and exudates improper collagen formation. Recently, developing a wound dressing material using MBNCPs has gained applicational significance due to their antimicrobial, good healing, biodegradability, and biocompatibility properties. The use of MBNCPs—based on chitosan biopolymer—is well known in wound dressing and healing applications. Sudheesh Kumar et al. [140] fabricated a wound dressing composed of chitosan hydrogel combined with nanozinc oxide bionanocomposites, which is used as a bandage for cooling sensation and moisture in the wound with a high protective barrier against microbes. In a recent study, the hydrogel of chitosan-based zinc oxide bionanocomposites was enhanced by castor oil polymeric films that display great potential as a wound dressing material [141]. Similarly, Zhai et al. [142] also demonstrated the effectiveness of keratin and chitosan-based nanozinc oxide bionanocomposite hydrogel in the antimicrobial treatment and as a potent candidate for wound healing. In an attempt to develop an ideal wound dressing material, Luo et al. [23] fabricated a new zinc oxide bionanocomposites based on bacterial cellulose that showed better results in wound healing and effective potential against microorganisms pathogens. Moreover, the silver-based biopolymer bionanocomposites have gained impressive use in wound healing and various biomedical applications [131].

In addition, recent advances to developing MBNCPs based on immunotherapeutic vaccines have been used as an alternative to traditional vaccines. The immunomodulatory nature of zinc oxide bionanocomposites has been developed to enhance the antigen presentation to CD4 and CD8 immune cells by an efficient antigen delivery. Sharma et al. [143] showed a robust intracellular vaccine delivery composed of zinc oxide nanowires coated by an exogenous peptide and generated more apoptotic stress on cells. Likewise, the uptake of ovalbumin loaded by zinc oxide nanosphere bionanocomposites also stimulates cancer immunotherapy [144]. Furthermore, to promote the adhesion and the hemocompatibility of implants and artificial organs, a promising approach based on preendothelialization is taking place where MBNCPs were developed to enhance the long-term hemocompatibility of artificial blood-contacting surfaces and prevent thrombotic effects. Hess et al. [145] synthesized a thermoplastic polyurethane loaded with gold or platinum bionanocomposites via the laser ablation method. Results showed that MBNCPs promote the generation of nonthrombogenic and noninflammatory preendothelialized surfaces.

The use of thermoresponsive polymers in dental decay presents a perfect application due to their ability to change under the variation of oral cavity temperature. Tempesti et al. [146] fabricated smart MBNCPs formed of poly(*N*-vinyl caprolactam) and poly-*N*-isopropyl acrylamide embedded with hydroxyapatite nanoparticles that demonstrated a better filling of dentinal tubules, maintaining the structure and thermal responsiveness as displayed in Fig. 7.10.

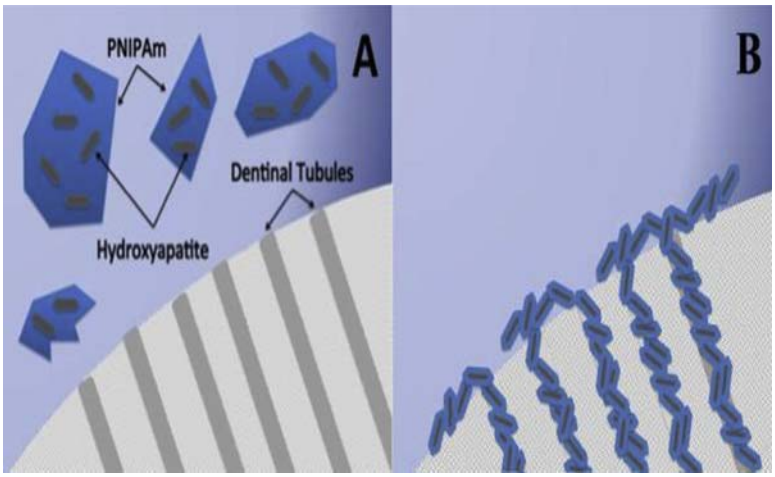

Figure 7.10

Poly(*N*-isopropylacrylamide)—hydroxyapatite nanocomposites as thermoresponsive filling materials ("A" at 25°C, "B" at 37°C) on dentinal surface and tubules. *Copyright 2018, Elsevier B.V. From P. Tempesti, G.S. Nicotera, M. Bonini, E. Fratini, P. Baglioni, Poly(N-isopropylacrylamide)-hydroxyapatite nanocomposites as thermoresponsive filling materials on dentinal surface and tubules, J. Colloid Interface Sci. 509 (2018) 123—131.*

5. Conclusion

Among various bionanocomposites, MBNCPs have been demonstrated to be the most extensively used due to their biocompatibility, biodegradability, nontoxic nature, long-term stability, and bioavailability. Multiple synthesis methods have been taken to assure the uniform dispersion of the nanofiller within the matrix and given potential properties. MBNCPs showed a great photocatalytic activity under visible and UV light where they performed various oxidation and reduction reactions. Consequently, numerous studies have reported excellent results regarding the use of photocatalytic MBNCPs in biomedical sciences as nanocarrier, bone scaffold, biomedical dressing, etc. Giving these results, MBNCPs may show promising potential to resolve the recent pandemic outbreak. Despite the hopeful applications of MBNCPs, there are remaining most important challenges related to their synthesis, formation, and their maximum target functionalities. In addition, their photocatalytic activity under UV light is still challengeable due to the side effects on the human body. Hence, further research is required to develop more efficiency of MBNCPs to extend on visible light for more safety and to improve their applications.

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CHAPTER 8

Bionanomaterials for wound healing applications

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List of abbreviations

ALP	alkaline phosphatase
BC	bacterial cellulose
BMP-2	bone morphogenic protein
BMPs	bone matrix proteins
BMSC	bone marrow mesenchymal stem cells
BNC	bacterial nanocellulose
CAE	computer-aided engineering
CANT	continuously aligned nanofibers threads
CEN	European Committee for Standardization
CMA	carboxylated or carboxymethyl agarose
CNCs	cellulose nanocrystals
CNFs	cellulose nanofibrils
CNWs	cellulose nanowhiskers
COX	cyclooxygenase
CPC	calcium phosphate cement
ECM	extracellular matrix
EGF	epidermal growth factor
ERK	extracellular receptor kinase
FGF	fibroblast growth factor
GAG	glycosaminoglycans
hABM-MSC	human alveolar bone marrow−derived mesenchymal stem cell
HGF	hepatocyte growth factor
HSE	human skin equivalent
IL-1β, IL-6, IL-10	interleukins-1beta, -6, or -10
iNOS	inducible nitric oxide synthase
MCC	microcrystalline cellulose
MFC/NFC	micro- or nanofibrillated cellulose
MMPs	metalloproteinases
MSCs	mesenchymal stem cells
NCC	nanocrystalline cellulose

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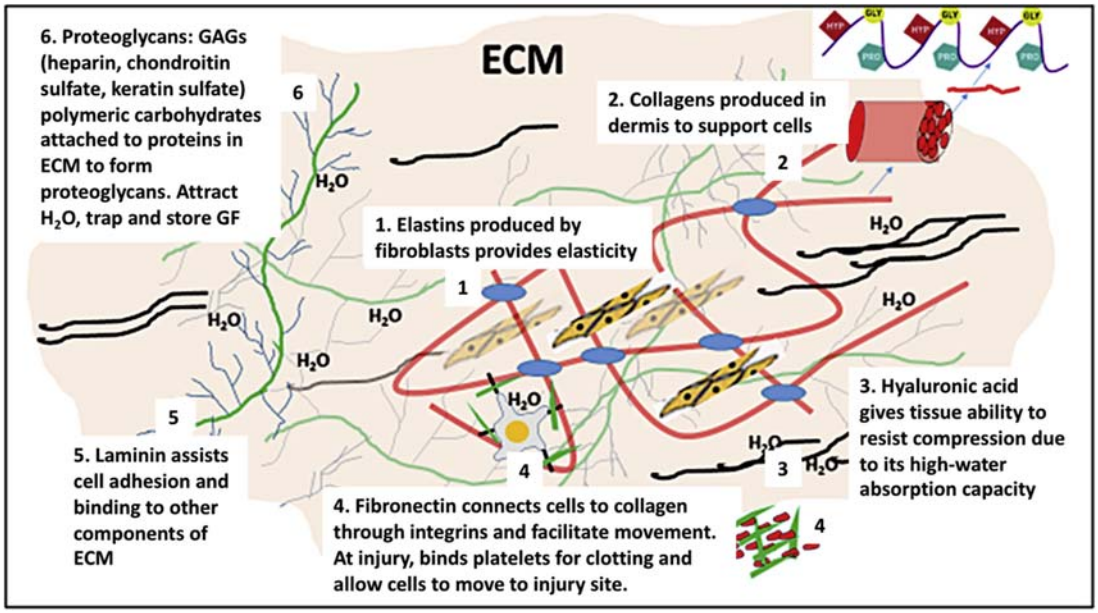
NF-kβ	nuclear factor kappa B
nHA	nanohydroxyapatite
NHOsts	normal human osteoblasts
PDGF	platelet-derived growth factor
PSuc	polysucrose
RGD	arginine−glycine−aspartic acid
SAP	self-assembling peptide
TGF-β	transforming growth factor-β
TIMP-1	TIMP metallopeptidase inhibitor 1
TNF-α	tumor necrosis factor-alpha
VEGF	vascular endothelial growth factor
α-TCP	α-tricalcium phosphate

1. Introduction

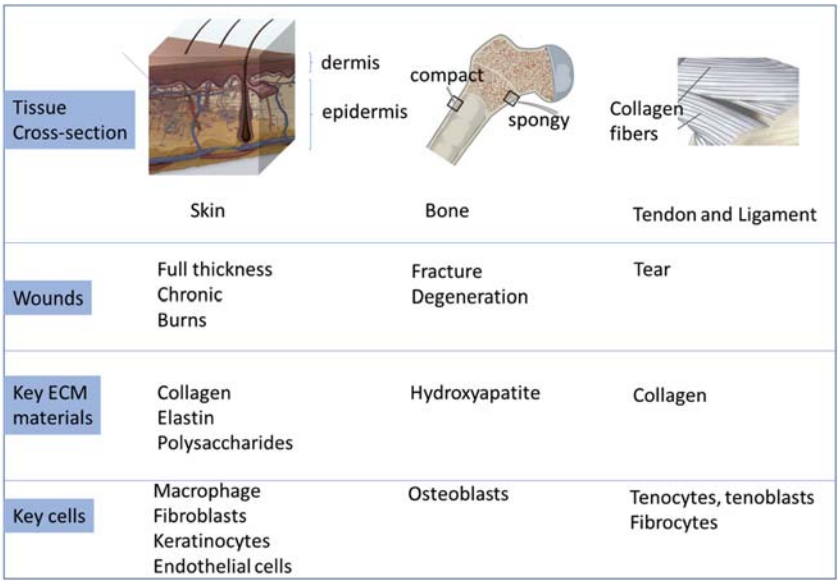
Injured tissue has an inherent mechanism for healing; however, the process is often difficult in the case of large, deep, or complex wounds to recover the original tissue with all its functionalities. Archeological findings have shown the use of human or animal bones and teeth, corals, shells, wood, and several metals as replacements for missing human bones and teeth [1,2]. The primary requirement of these scaffold predecessors for tissue regeneration after injury was bioinertness. Throughout the history of wound care, several strategies have been adopted to speed up or assist the wound healing process. The first generation of tissue engineering scaffolds provided a way to mimic the physical nano- and microstructures of the extracellular matrix (ECM) (Scheme 8.1) to allow cells to grow and form new tissue. Cells recognize microscale dimensions (10−100 μm), which influence cell behavior and migration. They interact with nanoscale proteins or components (for example, collagen fibrils, 50−200 nm diameter) of the ECM to proliferate and build new tissue. The discovery that the ECM consists of bionanomaterials with comparable characteristics to biopolymers available from land and marine resources gave a new impetus to scaffold engineering with the use of biomaterials to produce biomimetic scaffolds [3,4]. The latter resembles the native tissue in chemical composition, architectural features, and/or mechanical integrity. Thus, scaffolds not only have 3D nanostructures, but they can also mimic the biomaterials in the ECM. This has allowed the development of sophisticated wound care scaffolds, which can also include small natural molecules to target specific molecular mechanisms of wound healing as well as secondary clinical factors such as infections.

A major challenge in scaffold engineering is the broadest range of wound types and conditions such as chronic diabetic wounds, burns, bone fracture, tendon, and ligament tear. Both the wound site and tissue type determine the composition and structure of scaffolds for accelerated and efficient wound healing (Scheme 8.2). For instance, in skin


ECM
6. Proteoglycans: GAGs (heparin, chondroitin sulfate, keratin sulfate) polymeric carbohydrates attached to proteins in ECM to form proteoglycans. Attract H_2O, trap and store GF
2. Collagens produced in dermis to support cells
1. Elastins produced by fibroblasts provides elasticity
3. Hyaluronic acid gives tissue ability to resist compression due to its high-water absorption capacity
5. Laminin assists cell adhesion and binding to other components of ECM
4. Fibronectin connects cells to collagen through integrins and facilitate movement. At injury, binds platelets for clotting and allow cells to move to injury site.
H_2O

Scheme 8.1

Representation of the extracellular matrix in skin. *Reproduced with permission from K.M. Kennedy, A. Bhaw-Luximon, D. Jhurry. Skin tissue engineering: biological performance of electrospun polymer scaffolds and translational challenges. Regen. Eng. Transl. Med. 3 (4) (2017) 201–214.*



Scheme 8.2

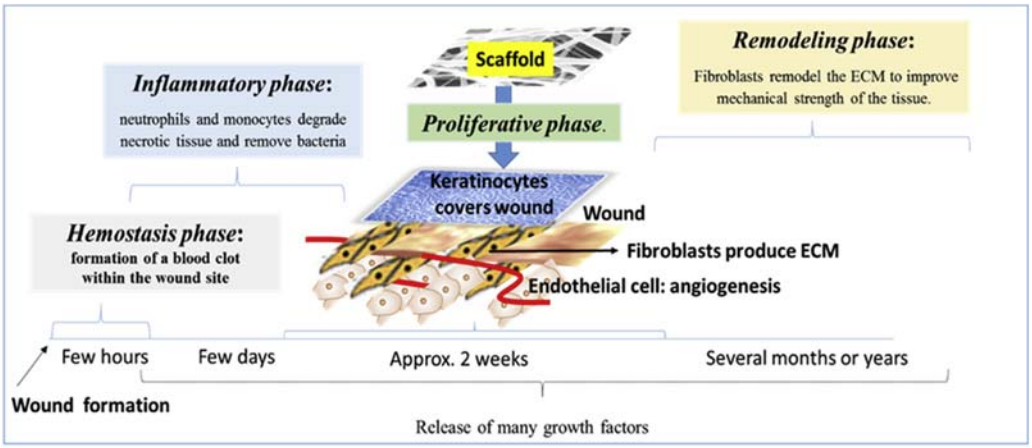
Types of wounds and key parameters.

tissue engineering (TE), the crucial parameters remain cell−scaffold interactions, rapid cell migration, differentiation, proliferation, and vascularization of regenerated tissue [6], whereas in tendon regeneration the use of collagen-based scaffold to mimic tendon tissue will target mechanical functionality of the repaired tendon [7]. Scaffolds for burn wounds are required not only for permanent burn wound coverage and scar reconstruction [8] but also for early closure and functional recovery of the skin as in the case of third-degree burn wounds [9]. Bone fracture scaffolds should, besides being porous and load-bearing, favor osteogenic differentiation, vascularization, and host integration [10]. Thus, the wound site and status guide the nanostructure and biomaterials in the scaffold for the efficient recovery of the original tissue.

2. Challenges of skin and skeletal tissue wounds

The three overlapping phases of wound healing for all types of wounds are the inflammatory (reactive), proliferative (reparative), and maturation (remodeling) phases. The type of wound will determine the duration of each of these stages. In diabetic wound healing, only the successful transition from the inflammatory phase to the proliferative phase will determine the efficient healing of the wounds [11]. Mesenchymal stem cell (MSC) homing during the proliferative phase plays a crucial role in bone fracture healing [12]. Collagen is continuously secreted by tenocytes and fibroblasts during the proliferative stage of tendon regeneration [13]. Ligament healing is also dependent on fibroblasts located between the rows of collagen fibers. They produce ECM containing proteoglycans, which store water essential to the viscoelastic properties of ligaments [14]. During the proliferative phase, immune cells release growth factors and cytokines to initiate fibroblast proliferation to rebuild the ligament tissue matrix. Thus, the main challenge in wound healing using bionanomaterials scaffolds is to be able to identify and interact positively with specific targets in the three stages of wound healing (Scheme 8.3).

Prolonged inflammation and excessive collagen deposition by macrophages and fibroblasts cause scarring during cutaneous wound healing (Scheme 8.4). [15]. Collagen III content is higher than collagen I in the early stages of healing, and during maturation, collagen III content decreases. Unwound skin and normal scar have a ratio of collagen I/III of 5:1 and 6:1, respectively, while a keloid scar has a ratio of 17:1. The less robust collagen I has an aligned structure while mature and flexible collagen III has a basket-weave structure due to cross-linking of the collagen chains. Thus, a scar can regain only up to 80% of the mechanical strength of healthy skin and is weak point in the skin barrier [16]. Scaffolds made from biomaterials have thus been shown to be able to control inflammation, and thus, collagen deposition consequently decreases scar formation.



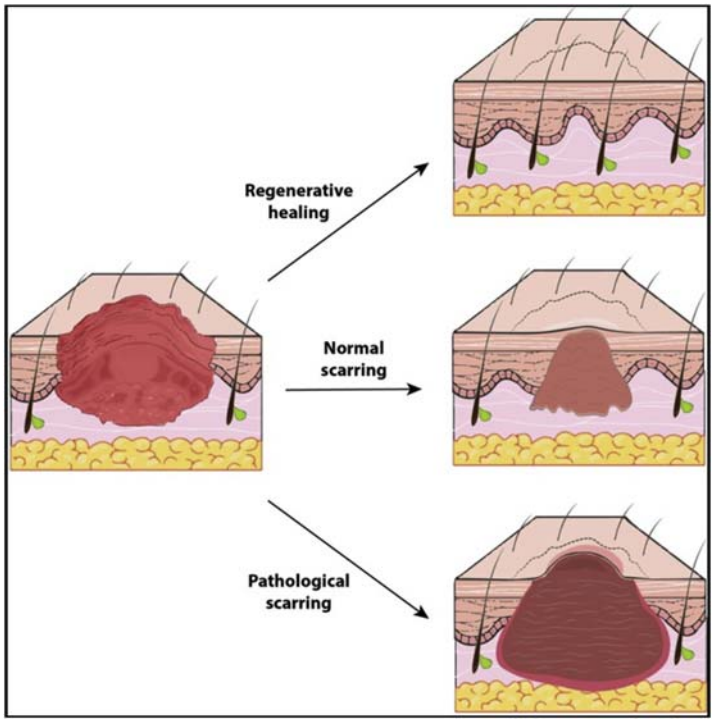
Scheme 8.3

Representation of cutaneous wound healing stages and the use of scaffolds. *Reproduced with permission from K.M. Kennedy, A. Bhaw-Luximon, D. Jhurry. Skin tissue engineering: biological performance of electrospun polymer scaffolds and translational challenges. Regen. Eng. Transl. Med. 3 (4) (2017) 201–214.*

2.1 Burns

The most common burn injuries result from flame and scald burns [18]. The temperature and extent of heat exposure determine the degree of damage to the skin, muscles, bones, and other organs. Temperatures were higher than 40°C causing coagulation necrosis in the human skin due to the denaturation of proteins. The burn wound depth determines its classification as first-, second-, and third-degree burn as well as its wound healing abilities (Scheme 8.5). Overall, the regenerative healing of the epidermis depends on keratinocytes migrating from healthy skin surrounding the wounds, and currently, the use of meshed split-thickness skin graft provides support for the keratinocytes to migrate and regenerate tissue [19]. There are three critical parameters in major burn injury, namely inflammatory response, infection, and scar formation.

During the inflammatory stage, several cytokines are secreted, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). The latter activates fibroblasts; however, prolonged activation of TGF-β causes wounds to contract to induce hypertrophic scars giving rise to disfigurement and deformity [20]. Thus the main aims of a scaffold for burn wound management would be to improve keratinization, decrease wound contracture, and improve vascularization.

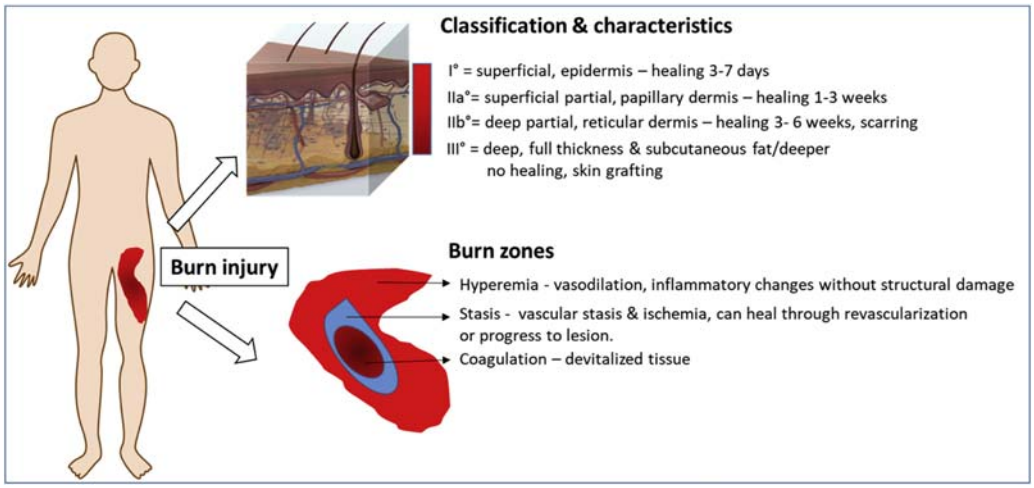


Scheme 8.4

The spectrum of human wound healing. *Regenerative healing* (top) is the "ideal" healing outcome and results in tissue that is indistinguishable from unwounded tissue. Typical adult cutaneous healing results in some fibrosis with the formation of a *normal scar* (middle), which contains collagen oriented in a dense, parallel alignment and does not regrow any dermal appendages (e.g., hair follicles). In certain instances, a *pathological scar* (bottom), such as a hypertrophic scar or keloid, may be generated. Compared with normal scars, these hyperfibrotic scars have even denser and more collagen, are more grossly apparent with increased discoloration, and may be pruritic or painful. *Reproduced from H.F. desJardins-Park, S. Mascharak, M.S. Chinta, D.C. Wan, M.T. Longaker. The spectrum of scarring in craniofacial wound repair. Front. Physiol. 10 (2019) 322.*

2.2 Diabetic wounds

Diabetic wounds unlike acute wounds have a prolonged inflammatory phase and fail to transition to the proliferative phase, thus giving rise to nonhealing chronic wounds [21]. For this transition to occur, the macrophages have to move from the M1 (proinflammatory) to the M2 (antiinflammatory) phenotype (Fig. 8.1). The latter allows the recruitment of fibroblasts and subsequently ECM formation, resulting in granulation tissue, which in turn promotes angiogenesis. The major components of granulation tissue are procollagen, elastin, proteoglycans, and hyaluronic acid [22].


Classification & characteristics
I° = superficial, epidermis – healing 3-7 days
IIa°= superficial partial, papillary dermis – healing 1-3 weeks
IIb°= deep partial, reticular dermis – healing 3- 6 weeks, scarring
III° = deep, full thickness & subcutaneous fat/deeper
no healing, skin grafting
Burn injury
Burn zones
Hyperemia - vasodilation, inflammatory changes without structural damage
Stasis - vascular stasis & ischemia, can heal through revascularization
or progress to lesion.
Coagulation – devitalized tissue

Scheme 8.5
Classification and characteristics of burns.

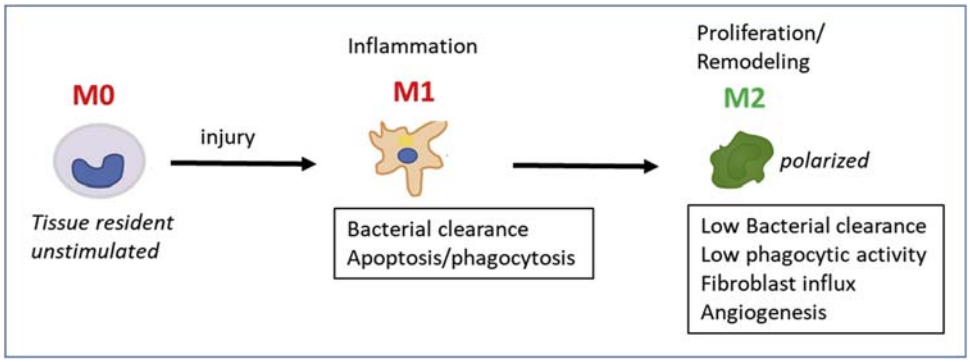


Figure 8.1
Role of macrophages at different stages of wound healing.

Thus the engineered scaffolds should be able to modulate the proteolytic activity of wounds inducing a shift from chronic to acute state. Thus, this promotes cellular migration, proliferation, matrix deposition, and recruitment of fibroblasts and angiogenic cells for the synthesis of granulation tissue [23]. Proteolytic activity is performed by proteases, particularly the matrix metalloproteinases (MMPs), which degrade and deposit ECM for wound healing [24]. A disruption of the degradation/deposit balance leads to chronic wounds with high levels of proteases and low levels of protease inhibitors. For instance, collagen and oxidized regenerated cellulose scaffold can bind and inactivate MMPs in chronic wounds. Collagen is a sacrificial substrate for the proteases, and the oxidized regenerated cellulose with its negative charge counteracts the positive charges of metal ions of MMPs, destroying their 3D structures [25].

Minimizing wound contraction in preventing scarring is also a desired outcome. Scarring is formed due to a prolonged inflammatory period, which increases fibroblast activity and thus promotes excessive deposition of ECM components such as immature collagen III. Healthy skin has a distribution of 80% collagen I and 15% collagen III located in the dermis.

2.3 Bone fracture

Bone is made up of the cortical or compact layer (outermost region) and the cancellous or spongy layer (inner section) (Fig. 8.2). Osteon fibers of 100−250 μm in diameter immersed in the interstitial matrix form the cortical or compact bone. Haversian canals (40−90 μm in diameter) and the randomly oriented Volkmann's canals (up to 50 μm in diameter) perpendicular to the Haversian canals are responsible for the porosity of bone. Osteocytes are mature osteoblasts embedded in the bone matrix during the formation phase of bone remodeling. Osteoblasts and osteoclasts form part of the surface of bone only over limited periods. Osteocytes produce growth factors and sclerostin, which promote and inhibit bone formation, respectively [26].

Bone tissue regeneration after injury is thus a complex process involving the recruitment of osteoprogenitor cells. The latter residing in the bone marrow gives rise to osteoblasts, which after maturational stages results in the mature osteocyte [28]. Bone fracture healing essentially occurs in four stages: hematoma formation, fibrocartilaginous callus formation, bony callus formation, and the remodeling phase (Scheme 8.6). Endochondral ossification occurs when the collagen-rich cartilage callus is converted to bone. Another important step

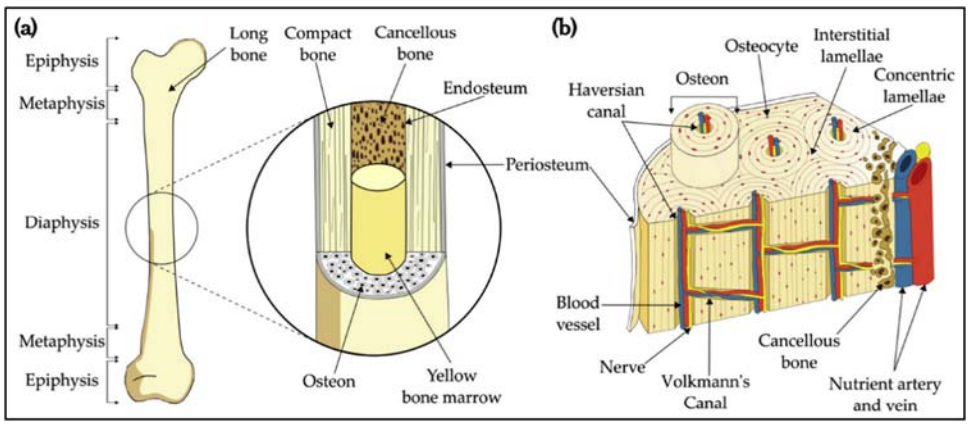
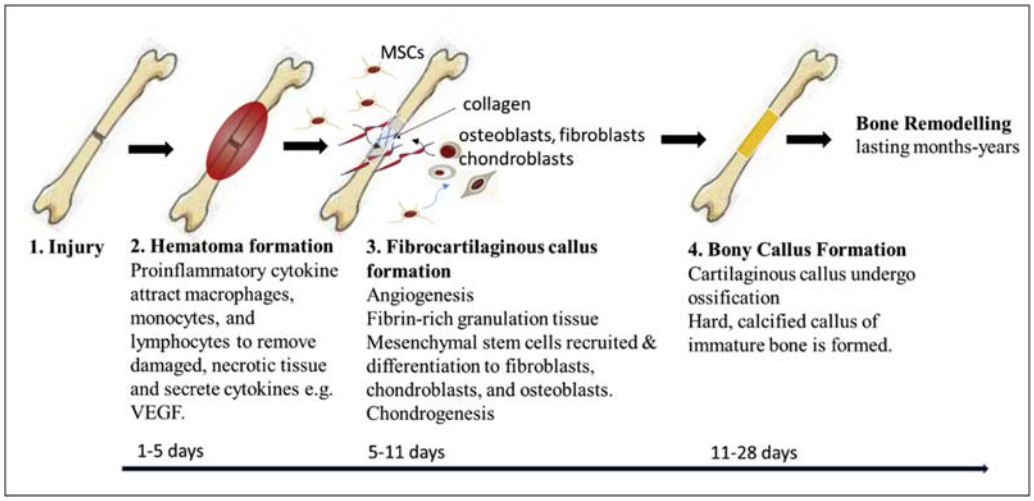


Figure 8.2

Schematic representation of (A) long bone and (B) microstructure. *Reproduced from J.A. Robles-Linares, E. Ramírez-Cedillo, H.R. Siller, C.A. Rodríguez, J.I. Martínez-López. Parametric modeling of biomimetic cortical bone microstructure for additive manufacturing. Materials 12 (6) (2019) 913.*



Scheme 8.6
Mechanism of fracture healing.

in the healing process is chondrogenesis. Mesenchymal cell condensation and chondroprogenitor cell differentiation give rise to chondrogenesis [29]. After cartilage formation, this is followed by chondrocyte hypertrophy and apoptosis to give rise to endochondral ossification.

2.4 Ligament and tendon damage

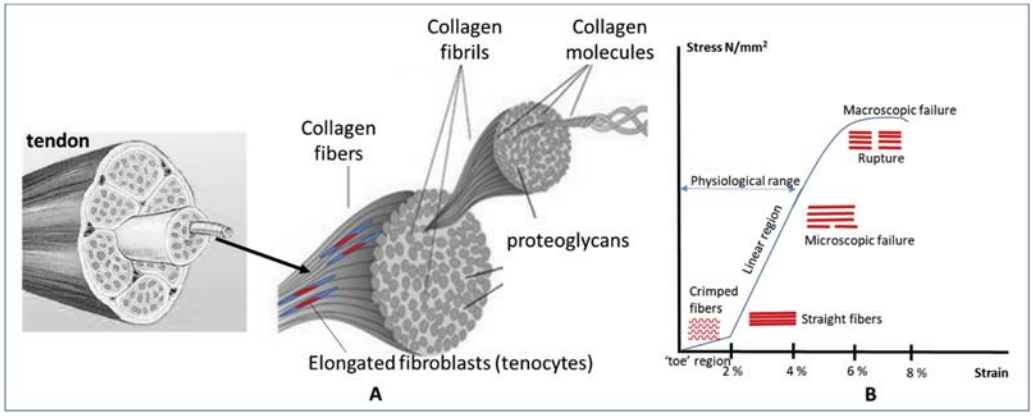
The main constituent of ligament and tendon is collagen (70%−80% dry mass) with collagen I being the most abundant. Tendons connect muscles to bones while ligaments connect bones to other bones [30,31] (Table 8.1). Proteoglycans bind water within tendons and ligaments, thus contributing to compressive properties and the lubrication of collagen fibers while glycosaminoglycan (GAG) filaments link collagen fibrils together.

There are several types of tendons and ligament injuries. The healing process follows the same three-stage process: inflammation, repair, and remodeling. During the repair stage, a tenascin C-rich matrix surrounds the mesenchymal progenitors, derived from the tendon's paratenon. A callus is formed with scleraxis-expressing cells to mature the repair tissue. In the remodeling stages, cells organize the collagen to produce the final repair tissue, which, however, has altered mechanics compared with the original tissue.

Micromechanical properties of tendon and ligament vary with location in the body, and the scaffold used for repair has to abide by the mechanics of these tissues [32]. They consist of a multiunit hierarchical structure composed of collagen molecules, fibrils, fiber bundles, fascicles, and tendon units (Scheme 8.7A). Thus, the development of scaffolds to repair

Table 8.1: Characteristics of tendons and ligaments.

Characteristics	Tendon	Ligament
Elasticity	Low	High
Tensile strength	High ~100–140 MPa	
Stiffness	Stiffness ~1.0–1.5 GPa	
Main cell type	Fibroblasts in continuous rows (tenocytes)	Scattered fibroblasts
Number	1 per muscle	Numerous per bone
Collagen fiber	Compact parallel bundles	Compact not arranged in bundles
Blood supply	High	Low
Types	1	Peroneal, fetal remnant and articular
Common injuries	Tendinitis (inflammation) Tendinosis (tear due to overuse) Achilles tendon injury Rotator cuff tendon	Anterior cruciate ligament injuries Collateral ligament injuries Posterior cruciate ligament



Scheme 8.7

(A) Hierarchical structure of tendons. (B) Typical stress–strain curve of tendons and ligaments.

ruptures remains a significant engineering challenge. For instance, in the native human tendon, a hydrated proteoglycan-rich matrix surrounds the collagen fibers, and thus, the water content in tendons is reported to be around 70%. This soft matrix phase binds the collagen fibers together, rather than collagen fibers weaving into each other, allowing the fibers to slide relative to one another, thus preventing damage associated with abrasion. The typical stress–strain curve of tendons and ligaments indicates that beyond a strain of 8%–10%, macroscopic failure occurs followed by rupture (Scheme 8.7B).

3. Nanobiomaterials used as scaffolds for skin and skeletal tissue regeneration

3.1 Cellulose-based scaffolds

3.1.1 Cellulose characteristics

The extensive use of synthetic polymers has been of great competition for the use of natural polymers in various fields including biomedical applications. However, cellulose is among the natural polymers that have been able to sustain this fierce competition mainly due to its key characteristics, namely, inexhaustible nature, high hydrophilicity, chirality, biodegradability (essentially by cellulose enzyme complex in microorganisms), broad chemical modifying ability, and its ability to generate versatile semicrystalline fiber morphologies, all of which bestow it with unique possibilities specific to biomedical applications (Fig. 8.3) [33]. Cellulose offers the ability to be converted into both micro- and nanoscale biomaterials through the use of chemical, enzymatic, and mechanical treatments, and the resulting biomaterials can be categorized into microcrystalline cellulose (MCC), micro- or nanofibrillated cellulose (MFC/NFC), cellulose nanofibrils (CNFs), cellulose nanocrystals (CNCs)/nanocrystalline cellulose (NCC) or whiskers, bacterial cellulose (BC), and nanocellulose (BNC) [34].

Cellulose is most commonly preferred due to its hydrophilicity, high reactivity, low fouling properties, renewability, nontoxicity, and compatibility with many organic and inorganic materials, which promote its use in hybrid materials and nanocomposites with unique properties such as wound dressing materials [35]. In addition, cellulose possesses hydrophilic hydroxyl moieties and specialized cellulose-binding domains, which promote the adhesion of cells to its surface [36]. Cellulose I (native cellulose) and II (regenerated cellulose) are the most commonly studied and used. The fascinating aspect associated with cellulose is that unlike other compounds forming hydrogen bonding, which are soluble in water, cellulose does not dissolve in the water despite possessing several hydroxyl groups involved in hydrogen bonding [37].

3.1.2 Skin tissue regeneration

Cellulose has been used in the form of both electrospun fibers and hydrogels for skin tissue regeneration, and in vitro/in vivo studies supported their excellent bioperformance (Table 8.2). Cellulose-based electrospun fibers used for skin TE include derivatives of cellulose, namely, cellulose acetate [38,39], hydroxypropyl cellulose, cellulose acetate propionate, and carboxymethyl cellulose [35]. Cellulose acetate is the most widespread derivative of cellulose, considered as a bio-based polymer by the European Committee for Standardization (CEN) [40], and has been used as nanofibrous scaffolds both alone and in composites for wound healing applications including diabetic foot ulcers [38,39,41,42].

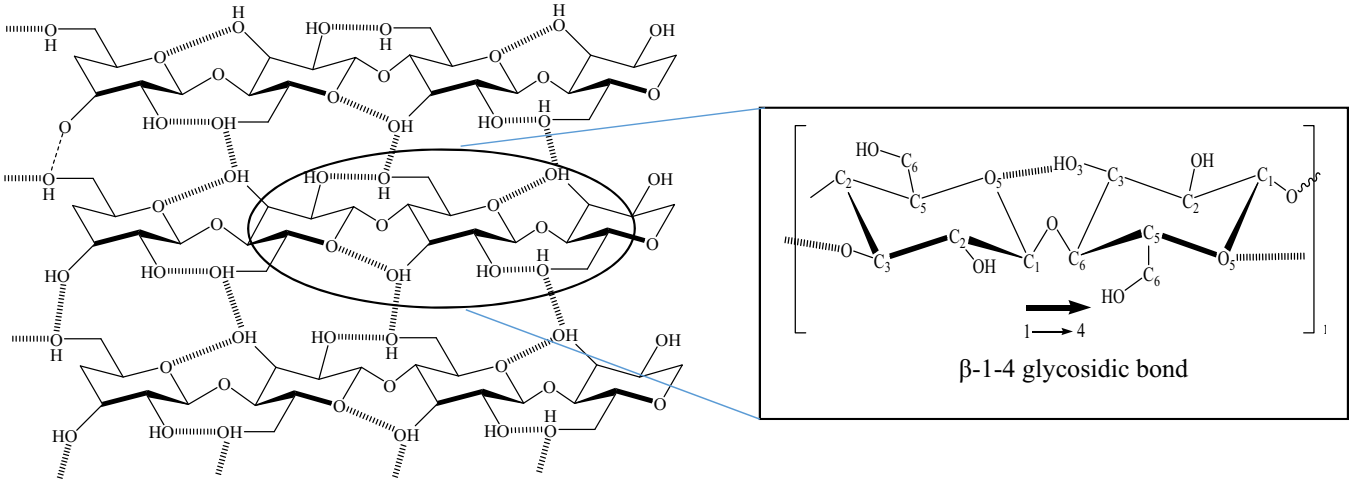


Figure 8.3
Hydrogen bonding in cellulose shows the β-1-4-glycosidic bond.

Table 8.2: Cellulose-based scaffold for skin tissue engineering applications.

Type of cellulose scaffolds	Wound type	Biological targets	Performance—In vivo/ In vitro
Nanofibrillar cellulose [54]	Burns	Antimicrobial activity, inflammatory response, integration of dressing to the wound	• Faster skin epithelialization than commercial Suprathel • Earlier self-detachment from the wound bed • Lack of inflammatory response and bacterial growth
Cellulose membranes regenerated from *Styela clava* tunics (freeze-dried) [55]	Surgical incision wounds	Angiogenesis	• Regulates angiogenesis and connective tissue formation which speeds up the healing process • Induces no specific toxicity
Oxidized regenerated cellulose/collagen (PROMOGRAN) with becaplermin [56]	Chronic wounds (diabetic foot ulcers)	Angiogenesis	• Controls wound proteases • Stimulates angiogenesis • Accelerates wound healing and closure • Reduces the frequency of dressing changes, thus more cost-effective
Cellulose/Soy protein nanofibrous scaffolds [57]	Excisional wound splinting model	Scar formation	• Enhances proliferation, migration, and infiltration of fibroblasts • Stimulates integrin-β1 expression • Accelerates reepithelialization and epidermal thinning • Decreases scar formation and collagen anisotropy
Nanofibrillar cellulose hydrogel (wood-derived nanocellulose) [58]	Full-thickness wounds	Wound contraction and scar formation	• Effectively impairs wound contraction in addition to the secondary contraction of a meshed split-thickness skin graft • Successful migration of keratinocytes from wound edges and reepithelialization in the wound bed
Bamboo cellulose nanocrystals with silver nanoparticles [59]	Full-thickness wounds	Angiogenesis Antibacterial and antiinflammatory	• Reduces the production of inflammatory cytokines • Promotes fibroblast proliferation, angiogenesis, and collagen deposition • Early tissue neoepithelialization and regeneration (less than 14 days)

Continued

Table 8.2: Cellulose-based scaffold for skin tissue engineering applications.—cont'd

Type of cellulose scaffolds	Wound type	Biological targets	Performance—In vivo/ In vitro
Nanocellulose films (wood-derived nanocellulose) [60]	Chronic wounds such as chronic venous leg ulcers	Antibacterial prevention and treatment of biofilm development	• Inhibits bacterial growth and promotes bacterial cell death more than commercial Aquacel • Decreases ability to develop biofilm • Contrasting morphology of bacterial cells on Aquacel and nanocellulose films, cells on Aquacel appear more healthy and less stressed
Bacterial cellulose [61]	Superficial partial-thickness burns	Bacterial infection, inflammatory response, and cell proliferation	• Provides a moist environment stimulates cellular growth and is effective in pain reduction • Complete epithelialization in 2 weeks • Shields against bacterial infections
Bacterial cellulose [62]	Diabetic foot ulcers	Bacterial infection, cell proliferation, and wound closure	• Good adherence of bacterial cellulose dressing to the wound, lesser pain, and dissipation of exudate • Wounds treated with bacterial cellulose dressing (32 days) healed faster than with Xeroform Petrolatum gauze (48 days) • 1.7 times higher rate of wound closure of bacterial cellulose treated wounds compared with Xeroform-treated wounds • Ability to overcome the initial inertia in the healing of larger wounds leading to the accelerated rate of healing and thus, complete wound closure

Cellulose scaffolds as wound dressings not only protect wounds but also deliver antibiotic drugs to inhibit the incidence of bacterial growth especially *Staphylococcus aureus* and *Escherichia coli* usually present in wounds [43–45]. The use of BC is preferred due to its features such as high purity, biocompatibility, biodegradability, highly porous architecture,

high swelling capacity, and high mechanical strength in swollen states, which, thus, substantiate its early use for wound healing applications since the 1980s [46]. The fibrillar structure of BC exhibits the ability to mimic the ECM component of human skin, most specifically collagen [47]. Hence, this justifies its use as tissue scaffolds for burn wounds and also for being the subject of extensive studies as a material apt for tissue regeneration in wounds. The required characteristics of an ideal wound dressing should include the ability to promote gaseous exchange, maintain a constantly moist environment for suitable wound hydration, accelerate the healing process, decrease the influence of debris on the healing process, offer protection to the newly regenerated tissues, and aid to attenuate the pain and discomfort associated with wearing and changing of the dressing [48]. BC can be thus be considered as a very effective wound dressing owing to its noncytotoxic nature in vivo, ability to exhibit high water vapor permeability due to the presence of numerous hydroxyl groups, ability to stimulate cell adhesion due to its optimal three-dimensional structure, its good flexibility, high water retention capability, and gaseous exchange owing to its microfibrillar structure [49,50]. BC does not possess any antibacterial potential by itself, and thus, it is used in combination with antibacterial compounds or biopolymers (e.g., chitosan) for antibacterial effect [46,51]. The highly porous nature and water holding capacity of BC allow the loading of drugs and bioactive molecules, thus acting as a drug delivery system of controlled release and simultaneously sustaining a physical barrier against bacterial infection and also reducing pain [48,50]. BC can maintain a desired moist environment in the never dry state. Wet conditions have been consistently reported as being optimal for speedy healing through accelerated reepithelialization, protection of the wound from infection, and pain reduction since it inhibits the adhesion of dried dressing to the wound [52]. BC was also found to promote absorption of exudate and necrotic tissues, thus enhancing fibrinous clotting application [53].

3.1.3 Bone tissue regeneration

Cellulose is a very versatile polymer that can be adapted to satisfy the requirements of the rigid and mechanically demanding biological environment of bones [36]. Different types of cellulose have been applied to bone tissue engineering, namely, plant, algal, and bacterial cellulose [63]. However, similar to wound healing applications, BC has been the most widely investigated for bone tissue regeneration. Its suitability for bone regeneration was primarily based on its excellent mechanical properties, microporosity, unique surface chemistry, and its low degradation rate allowing for timely osseointegration [64]. The morphology of BC is based upon a fibrillar structure, which mimics the collagenous fibers of bone and also, the surface of the microfibers acting as the adhesion site for cells, provide mechanical stability and structural guidance in the process of bone formation [65]. BC has often been studied in combination with other bone repair components, including hydroxyapatite, bone marrow mesenchymal stem cells (BMSCs), growth factors, ECM protein, and estrogen to enhance the ability of bacterial composites in the bone repairing

process [66]. BC nanofibers in composite with hydroxyapatite were reported to mimic natural bone with similar porous architecture, mechanical strength, and biocompatibility [36]. The mineralized BC-based scaffold increased cellular activity and biomineralization indicating the applicability of BC and its composites in bone tissue engineering applications [36]. Plant cellulose has been used in the form of cellulose nanowhiskers (CNWs), CNCs, or CNFs as reinforcing materials in electrospun nanofibers, as they greatly improve the mechanical properties due to their highly crystalline nature and their ability to orient along the fiber axis producing unidirectional fiber-reinforced composites [35]. In contrast to metal and carbon-based nanofillers, CNCs are biodegradable, biocompatible, and nonecotoxic and possess high crystallinity, high mechanical strength, and a large surface area [35]. The incorporation of nanocellulose in both 2D and 3D synthetic or natural polymer matrices has gained increasing interest in bone TE since the scaffolds were found to exhibit improved mechanical properties, increased wettability, osteogenic potential, osteogenic differentiation, osteoconductive properties, strong effect on directing the cellular organization, and higher ability to support the growth of hydroxyapatite [67–71].

3.1.4 Ligament and tendon regeneration

Limited work has been conducted on the use of cellulose for ligament and tendon regeneration. It has been mainly used in the form of fibrous nanocomposite scaffolds for ligament and tendon regeneration. Aligned polycaprolactone/chitosan/CNC (PCL/CHT/CNC) nanocomposite fibrous scaffolds were reported to exhibit mechanical properties (tensile strength of 39 ± 2 Pa and Young's modulus of 541 ± 84 MPa) in the range of tendon tissues (5–100 MPa and 20–1200 MPa), which maintained the phenotype of the human tendon–derived cells (hTDCs) seeded on the scaffolds [72]. The PCL/CHT/CNC nanoscaffolds presented topographic cues for maintenance of the tendon cell morphology and behavior [72]. This nanocomposite was utilized in the form of continuously aligned nanofibers threads (CANT), assembled into woven 3D hierarchical scaffolds that displayed tendon/ligament nano-to-macroarchitecture, nanotopography, and nonlinear biomechanical behavior that stimulated a high cytoskeleton elongation, an anisotropic organization characteristic of tendon tissues [73]. Another study focused on the mechanical properties of cellulose nanofibrous scaffolds in simulated body conditions after sterilization with gamma rays [74]. The nanoscaffolds not only matched the mechanical requirements of ligaments and tendons but also proved to exhibit a stable performance toward cyclic loading and unloading in addition to the positive response to the proliferation and differentiation of both human ligament and endothelial cells [74].

3.2 Seaweeds polysaccharide-based scaffolds

Seaweeds or macroalgae are widely abundant marine organisms that produce bioactive compounds such as polyphenols, peptides, proteins, lipids, and polysaccharides with

numerous health benefits [75]. They are classified as green algae (Chlorophyta), brown algae (Phaeophyceae), and red algae (Rhodophyta) according to the color transmitted by their nature and combination of their dominant pigments. Seaweeds polysaccharides, such as fucoidan, alginate, carrageenan, agarose, and ulvans with unique structural and functional entities, possess inherent features that can mimic the ECM [76] (Table 8.3).

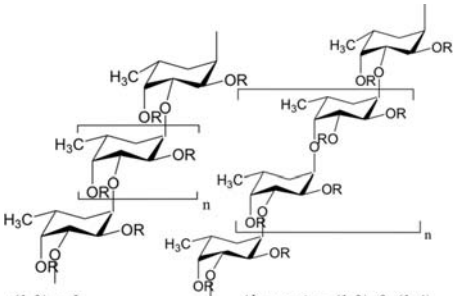
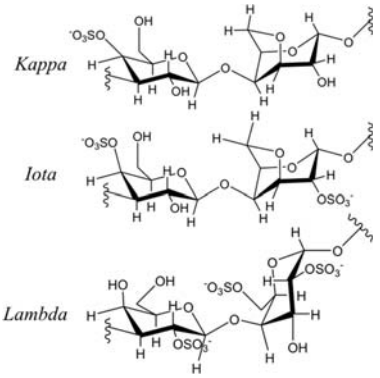
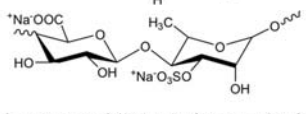
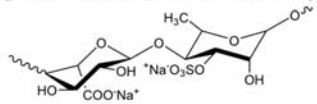
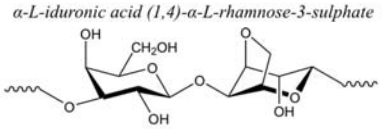
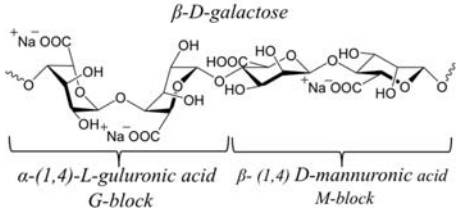
Agarose and carrageenan possess thermoreversible gelling properties, exhibiting sol−gel transition upon cooling (Fig. 8.4). Agarose self-gels as their random coil conform to double-helix aggregates via inter- and intramolecular hydrogen bonding by cooling in physiological temperature [77]. The final sol−gel transition of carrageenan leading to helix−helix aggregation occurs in the presence of cations, which bond adjacent spiral chains with sulfate groups. Similarly, ulvans had also shown thermoreversible gelling properties in the presence of cations at basic pH. On the contrary, little has been reported on the gelling properties of fucoidan requiring a minimum concentration of 25% to initiate gelation when combined with other polymers with opposite net charge [78]. Alginate is more susceptible to ionic gelation in the presence of bivalent and trivalent cations such as Ca^{2+}, Cu^{2+}, Zn^{2+}, Ba^{2+}, and Sr^{2+}, which bond to blocks of alginate polymers in a planar 2D manner referred to as the "egg-box" model [79].

3.2.1 Skin regeneration

Among all seaweed polysaccharides, fucoidan has shown promising skin tissue regenerative properties owing to its fucose and sulfate groups responsible for increased fibroblast migration and accelerated expression of integrin-α2β1 [80]. It has been shown to facilitate the formation of an adherent hematopoietic culture, which takes place through cell adhesion factors like L-selectin and integrin [81]. Fucoidan also possesses a heparin-binding domain that binds easily to growth factors such as fibroblast growth factors, FGF-1 and FGF-2, inducing the formation of the fibrillar collagen matrix, fibroblast proliferation, and in vitro and in vivo angiogenesis [82,83]. It has been shown to regulate the effects of transforming growth factor (TGF)-β1 on the proliferation of fibroblasts and the repopulation of wounds in vitro [76]. Fucoidan-infused high water-content dressings were found to be effective in diabetic wound healing [84]. Similar to fucoidan, ulvans also exhibit cell adhesive properties in addition to their antiinflammatory and attractive skin-related properties such as inhibition of bacterial adhesion to the skin and protecting against UV-induced and age-related damage. Ulvans possess rhamnose parts recognized by α-L-rhamnose-specific lectin site of human skin keratinocytes and fibroblasts, which induced cell proliferation and ECM biosynthesis [85].

Alginate is the most reviewed seaweed polysaccharide in the form of hydrogels, microspheres, sponges, and fibers for tissue regeneration [79,86−88]. However, unlike sulfated polysaccharides, it is known to absorb few proteins and lack cell adhesive properties. Thus, alginate cross-linked with cationic polysaccharides such as chitosan and

Table 8.3: Seaweeds polysaccharides and their chemical structure and source.

Seaweeds polysaccharide	Chemical structure	Seaweed genus and species
Fucoidan	 *(1,3)-α-L-fucopyranosyl* *Alternating (1,3) & (1,4)-α-L-fucopyranosyl*	**Brown algae** *Sargassum (fusiforme; horneri)* *Fucus (evanescens; serratus; vesiculosus)* *Laminaria (digitate; japonica; hyperborean)* *Pelvetia canaliculata* *Cladosiphon okamuranus* *Nemacystus decipiens* *Padina gymnospora* *Ascophyllum nodosum*
Carrageenan	 *Kappa* *Iota* *Lambda*	**Red algae** *Eucheuma (denticulatum; cottonii also known as Kappaphycus alvarezii)* *Chondrus crispus* *Sarcothalia crispata* *Gigartina (acicularis; pistillata; radula)* *Hypnea musciformis* *Mastocarpus stellatus*
Ulvan	 *β-D-glucuronic acid (1,4)-α-L-rhamnose-3-sulphate*  *α-L-iduronic acid (1,4)-α-L-rhamnose-3-sulphate*	**Green algae** *Ulva (arasakii; armoricana; clathrate; compressa; conglobate; fasciata; gigantea; intestinalis; lactuca; linza; meridionalis; ohnoi; olivascens; pertusa; prolifera; rigida; scandinavia; rotundata)*
Agarose	 *(1,4) linked 3,6 anhydro-α-L-galactose and (1,3) linked β-D-galactose*	**Red algae** *Gelidium* *Gracilaria*
Alginate	 *α-(1,4)-L-guluronic acid G-block* *β- (1,4) D-mannuronic acid M-block*	**Brown algae** *Macrocystis pyrifera* *Laminaria (ochroleuca; japonica; hyperborea; digitata)* *Ascophyllum nodosum* *Alaria esculenta* *Lessonia* *Ecklonia* *Eisenia* *Nereocystis* *Sargassum* *Cystoseira* *Fucus*

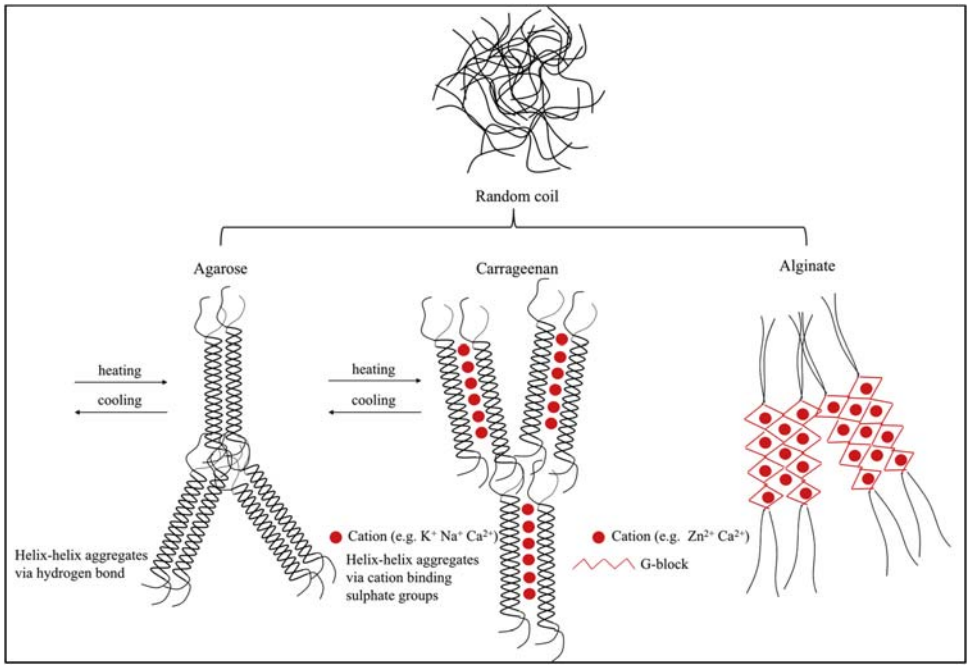


Figure 8.4
Gelling mechanism of seaweed polysaccharides, such as agarose, carrageenan, and alginate.

gelatin in an ionic solution of calcium chloride has been widely investigated. The negatively charged carbonyl group (−COOH) of alginate binds with the positively charged amino ($-NH_3^+$) group of chitosan/gelatin to form structurally stable scaffolds to support cell growth [89]. Alginate can also be covalently cross-linked with gelatin/chitosan via Schiff-based reaction between aldehyde groups of oxidized alginate and an amine group of chitosan/gelatin [90]. Balakrishnan et al. reported in situ forming alginate-dialdehyde/gelatin hydrogel cross-linked in the presence of borax susceptible to faster biodegradation unlike calcium cross-linked alginates [91]. While chitosan has been shown to increase cell adhesion and collagen type I production on fibroblast seeded alginate−chitosan hybrid polymer fiber, gelatin composed of RGD sequences improved in vitro proliferation of L929 mouse fibroblasts seeded on freeze-gelled alginate/gelatin scaffold [92,93]. Collagen can also act as cell adhesion ligand and has been grafted on poly(vinyl alcohol)/gelatin/alginate electrospun mats, improving the hydrophilicity and cellular adhesion of the mat [94]. Alginate or alginate−chitosan has been combined with other polymers such as polyvinyl alcohol, hyaluronan, cellulose, and fucoidan to form composite scaffolds with tunable physiochemical and biological properties [95−98].

Agarose has been shown to impart thermosensitivity to the chitosan and alginate to form in situ thermoresponsive injectable hydrogels suitable for non-invasive wound healing

applications [99,100]. In addition to their thermosensitive properties, agarose hydrogels based on carboxylated or carboxymethyl agarose (CMA) derivatives also exhibit pH-responsive properties [101,102]. Recently, CMA hydrogels encapsulating silver ions accelerated wound closure in BALB/c mice due to sustained release of silver ions with antibacterial properties in the wound environment at acidic pH via disruption of ionic interactions between silver ions and deprotonated carboxymethyl groups [103]. Another pH-responsive agarose hydrogel is based on agarose-ethylenediamine forming dynamic Schiff-base linkages with dialdehyde-functionalized polyethylene glycol [104]. Carboxylated agarose has also been electrospun in ionic liquid 1-butyl-3-methylimidazolium chloride to form mechanically stable micron-sized fibers with antimicrobial properties [105]. However, the limited solubility of agarose and its derivatives in solvents other than water is known to compromise their spinnability.

3.2.2 Bone regeneration

Sulfated polysaccharides, such as fucoidan, ulvans, and carrageenans, have shown high osteoconductive properties. Fucoidan was found to favor the production of alkaline phosphatase (ALP) and type I collagen as well as upregulate bone morphogenic protein (BMP)-2 and promote osteocalcin and mineral deposition associated with bone mineralization [95]. Fucoidan also improved osteogenesis and induced osteogenic differentiation in human adipose-derived stem cells and human amniotic fluid stem cells, making it a suitable material for bone regeneration [106]. Similarly, ulvan-based hydrogels, mainly investigated for bone tissue regeneration, were shown to stimulate mineral formation, which enhanced osteogenic activity and differentiation of cells [107,108]. Carrageenan-based hydrogels exhibiting structures bearing similarity to the ECM, also stimulated the formation of bone-like apatite and promoted cellular activities [109–112].

However, the mechanical limitations of seaweed polysaccharide-based scaffolds have been a major challenge in bone tissue regeneration [113]. Derivatized forms of carrageenans such as over sulfated, acetylated, phosphorylated, oxidized, carboxymethylated, and methacrylate were shown to form structurally stable carrageenan-based hydrogels [114]. Additionally, a wide range of reinforced scaffolds based on seaweed polysaccharides, including fucoidan, carrageenans, alginate, and agarose combined with an inorganic phase, such as hydroxyapatite, have been reported [81–83,106,115,116]. Agarose hydrogels have shown characteristics for biomineralization [117–122]. Injectable HAp/agarose gel regenerated a rabbit femoral bone defect within 4 weeks, followed by complete resorption 8 weeks postimplantation [123]. Mechanically stiff agarose/HA nanocomposite inducing high proliferative and ALP activity of MG63 osteoblasts, has also been fabricated via in situ precipitation method for load-bearing bone substitute [124].

As for alginate, various reinforcing materials including graphene oxide, calcium silicate, nanosilica, hydroxyapatite (HA), tricalcium phosphate (∝-TCP), and calcium phosphate cement (CPC) have been used for bone tissue regeneration [125–128]. Recently, nanohydroxyapatite (nHA) added to alginate–chitosan microspheres/microcapsules was shown to promote adhesion and proliferation of MG-63 human osteoblasts and induced high mineralization and ALP expression [129,130]. CPC was used combined with cell-loaded alginate microbeads or alginate–chitosan complex to form injectable bone substitutes [131,132]. The bioinert alginate scaffolds were also grafted with cell adhesion ligands to improve cell anchorage, specifically the arginine–glycine–aspartic acid (RGD) peptide sequence. An RGD peptide in conjunction with PHRSN (proline–histidine–serine–arginine–asparagine) sequence grafted on alginate gels promoted proliferation and differentiation of normal human osteoblasts (NHOsts) showing the highest cell number and osteocalcin production at 67% RGD content [133]. Alginate has also been combined with decellularized, demineralized bone ECM to form hydrogels for bone regeneration [134].

3.3 Sucrose-based scaffolds

Over the past two decades, sucrose, in its granulated, powdered, or paste form, has been extensively studied in clinics for treating chronic wounds, burns, and ulcers [135]. Direct application of sugar exhibiting hygroscopic properties exerts a local osmotic effect, which inhibits bacterial growth by lowering the pH and water activity of the wound exudate environment [135,136]. Sucrose has been shown to reduce edema in wounds and promote macrophage activation, granulation tissue formation, collagen synthesis in fibroblasts, and minimal scarring [135,136]. However, local hyperglycemia is counterintuitive for the treatment of wounds, which has been associated with one case of acute renal failure and hyponatremia though systemic adsorption of locally applied sugar is least expected [135]. Recently, wound dressing impregnated with a lipidocolloid matrix containing sucrose-octasulfate potassium salt (UrgoStart Contact) accelerated reepithelialization and wound closure of neuroischemic diabetic foot ulcers. The high charge density of sucrose octasulfate matrix potassium salt inhibits matrix metalloproteases and restores biological functions of growth factors [137,138].

A range of hydrogels from sucrose derivatives bearing vinyl groups such as sucrose acrylate and sucrose methacrylate have been synthesized [139]. However, despite major advances in TE over the past decade, studies on the wound healing potential of sucrose-based scaffolds are limited. Sucrose disaccharides are copolymerized by epichlorohydrin to form highly branched, semisynthetic polysaccharide, and polysucrose (PSuc) commercially available as Ficoll. It is known for its biocompatibility as a macromolecular crowding agent and density gradient centrifugation medium. Jugdawa et al. were the first

to report on the interactions of polysucrose-methacrylate hydrogels with NIH3T3 fibroblast cells [140]. The cells adhered and conformed to spindle-shaped morphology in the porous regions of the hydrogels. Polysucrose blended with poly-L-lactide and polydioxanone has been electrospun into nanofibrous mats and has shown to improve the in vitro proliferative activity of L929 fibroblasts and HaCaT keratinocytes. This study emphasized the balance between mechanical properties and hydrophilicity of the mats at tissue formation [141].

4. Peptide hydrogels for wound healing

Peptide-based hydrogels not only exhibit several of the essential characteristics of hydrogels to promote effective wound healing, in addition, but they also provide ECM-mimicking environments consisting of tissue-like amino acid sequences with highly ordered structures (Fig. 8.5) [15,142,143]. They are formed by either spontaneous hydrogenation, enzyme-controlled hydrogenation, or cross-linking-enhanced hydrogenation.

Since the serendipitous discovery of the first self-assembling peptide (SAP) EAK16 from the yeast *Zuotin* (Fig. 8.5A) [144], a new research area has opened up for applications of these molecules in tissue engineering and accelerated wound healing by their ability to self-assemble into well-ordered nanofibers and hydrogel scaffolds [145,146]. EAK16 and RADA16 (RADARADARADARADA) [144,147] are synthesized using natural L-amino acids by solid-phase chemistry and have alternating hydrophobic, e.g., alanine, valine, leucine, isoleucine, phenylalanine, and hydrophilic moieties, e.g., lysine, arginine, histidine, aspartic acid, and glutamic acid that render them water-soluble (Fig. 8.5A). Their initial use was as a substrate for 2D cultures and later 3D culture models as matrices to study cell behavior in in vivo like environment.

The peptides have been functionalized via their C-termini with specific motifs [152], to favor specific cell interactions in terms of cellular viability, migration, proliferation, and differentiation in wound healing. The peptide scaffolds have proved to be efficient also in promoting osteoblast growth and differentiation [153], in cartilage repair and cartilage tissue engineering [154], in supporting neuronal cell attachment, differentiation, and an extensive neurite outgrowth [155]. RADA-like hydrogels (Fig. 8.5C) [156], e.g., RADA16-I promoted mature bone formation in a calvaria bone defect in mice [157] and, when loaded with recombinant bone morphogenic protein (BMP-2), increased cortical bone regeneration in rabbits [158]. d-RADA16 hydrogels loaded with basic-fibroblast growth factor (bFGF) promoted bone repair in femoral condyle defects in rats [159].

SAP RADA16-I hydrogel scaffolds in combination with epidermal growth factor (EGF) gave rise to an increase in reepithelialization in a human skin equivalent model (HSE), which have many morphologic and phenotypic properties of human skin. Interestingly,

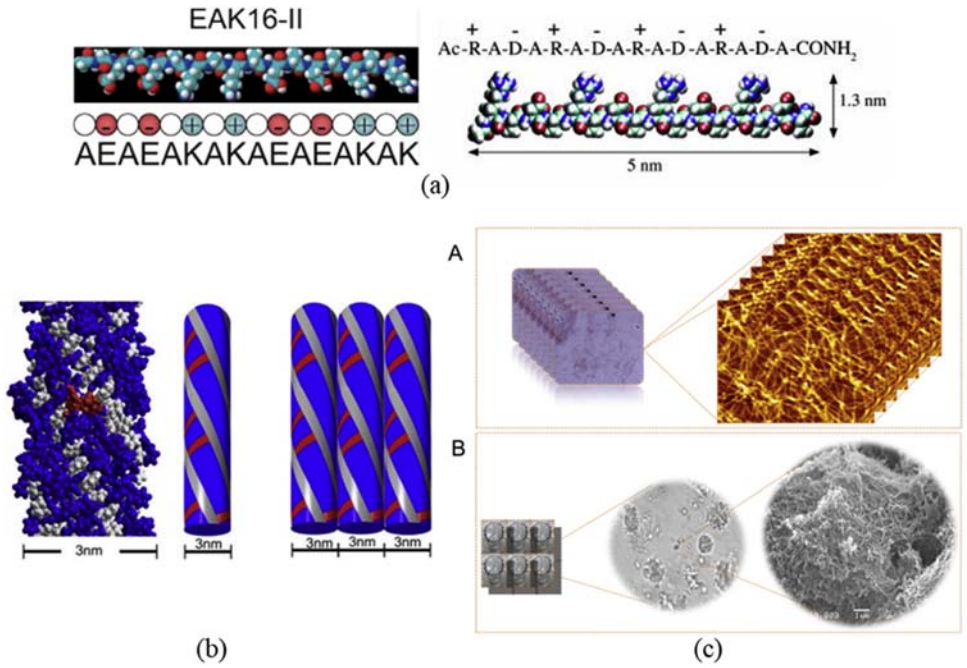


Figure 8.5

(a) EAK16 sequence. RADA16-I sequence. Copyright (2005) National Academy of Sciences, United States [149]. (b) Fibrillar structure of Fmoc-FF and Fmoc-RGD. (c) (A) microstructure and (B) macrostructure of d-EAK16 cultured in the 3D environment. *Reproduced with permission from (a)S. Jun, Y. Hong, H. Imamura, B.Y. Ha, J. Bechhoefer, P. Chen. Self-assembly of the ionic peptide EAK16: the effect of charge distributions on self-assembly. Biophys. J. 87 (2) (2004) 1249–1259; (b) M. Zhou, A.M. Smith, A.K. Das, N.W. Hodson, R.F. Collins, R.V. Ulijn, et al. Self-assembled peptide-based hydrogels as scaffolds for anchorage-dependent cells. Biomaterials 30 (13) (2009) 2523–2530; (c) Z. Luo, Y. Yue, Y. Zhang, X. Yuan, J. Gong, L. Wang, et al. Designer D-form self-assembling peptide nanofiber scaffolds for 3-dimensional cell cultures. Biomaterials 34 (21) (2013) 4902–4913.*

EFG was released from the hydrogel only when it is in contact with the wound, which closed 3.5 times faster than those treated with SAP scaffold without EGF. Short cross-linked cysteine-containing peptides, having between three and seven amino acids, also self-assembled spontaneously in water to form hydrogels [160]. These hydrogels were shown to be safe for use as a topical wound dressing and potentiated reepithelialization (Fig. 8.6).

Resveratrol-loaded short SAP hydrogels were shown to inhibit inflammatory cytokines TNF-α and IL-1β, thus accelerating wound healing and reducing scar formation [15]. Resveratrol activates the NAD-dependent protein deacetylase sirtuin 1 (SIRT1), which was found to induce hypertrophic scar formation via ECM proteins deposits. SAPs since the

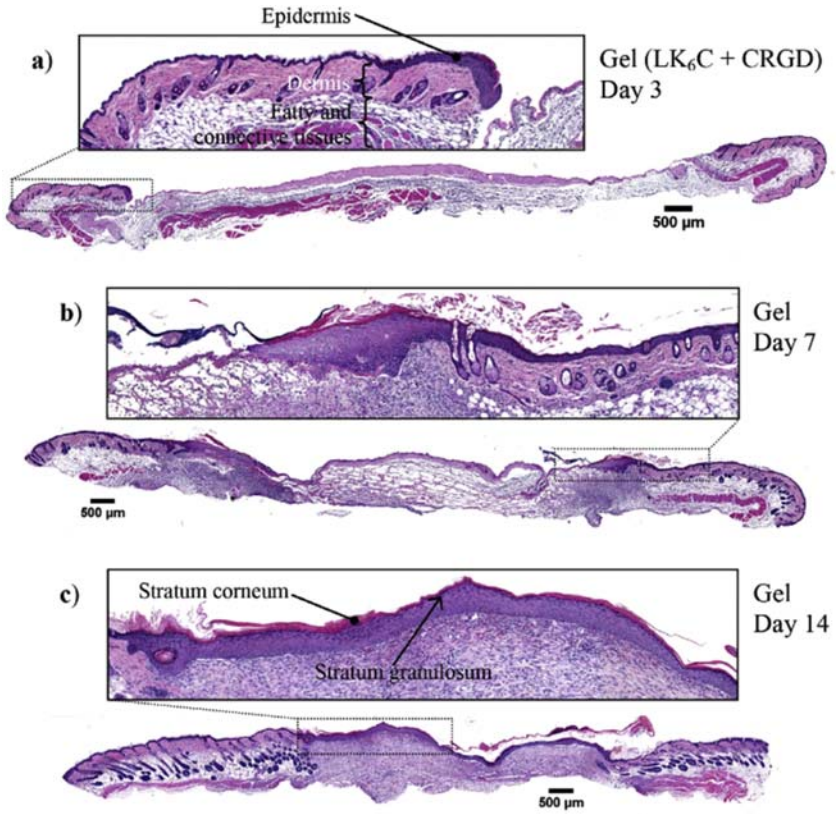


Figure 8.6

Representative cross-sectional histological sections of wounds treated with peptide hydrogel infused with complete medium. Skin samples were obtained on day (a) 3, (b) 7, (c) 14 for staining with H&E. Over time, the leading front of the epidermal "tongue" was observed to migrate inward to close up the wound and restore the critical barrier function of the skin. Reepithelialization was completed by day 14, along with the appearance of a visible layer of stratum corneum and stratum granulosum. All insets show magnified images of the respective boxed regions. *Reproduced from W.Y. Seow, G. Salgado, E.B. Lane, C.A. Hauser. Transparent crosslinked ultrashort peptide hydrogel dressing with high shape-fidelity accelerates healing of full-thickness excision wounds. Sci. Rep. 6 (2016) 32670.*

seminal publication of Zhang and their tissue engineering and reparative applications are now approved for use in accelerated wound healing in chronic diabetic ulcers (Figs. 8.7 and 8.8) [161].

Another interesting review summarizes the use of peptide-based materials that exhibit antimicrobial properties and can accelerate wound healing in DFU [162]. Peptide amphiphile sequences have been designed to specifically bind heparin and form nanofibers, and the presence of vascular endothelial and fibroblast growth factors leads to extensive blood vessel formation in vivo [163]. Bioactive heparin−mimetic peptide

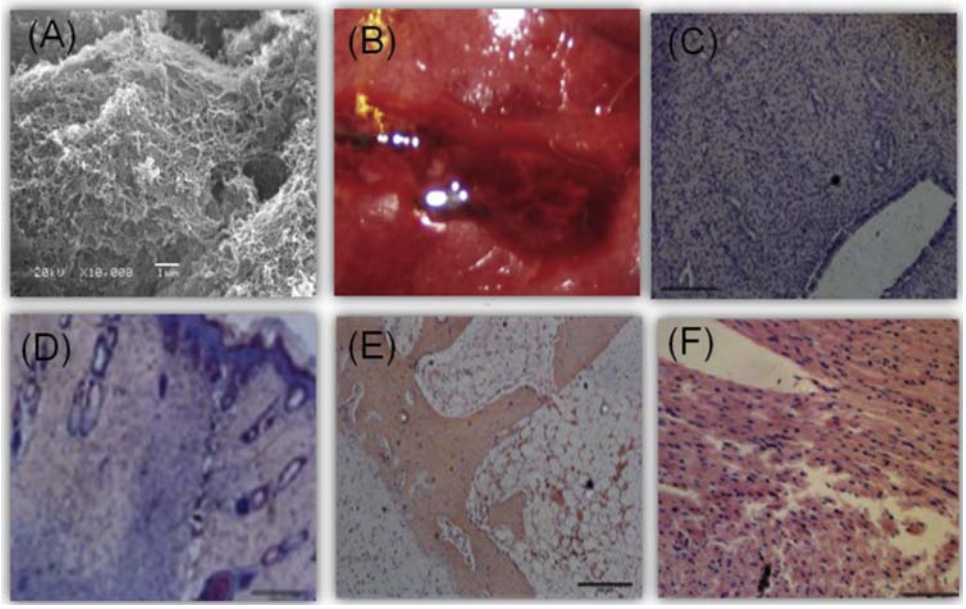


Figure 8.7
SAP is used in various areas. (A) Used in 3D tissue cell culture; (B) rapid hemostasis to stop bleeding; (C) accelerated rat skin wound healing; (D) accelerated rat uterus wound healing; (E) accelerated rabbit articular cartilage injury repair; (F) promotion of rat myocardial infarction repair. *Images courtesy of Zhongli Luo's laboratory.*

Figure 8.8
Use of SAP hydrogel in the chronic diabetic venous ulcer: I, before treatment; II, 2 days after treated; III, 16 days later the ulcer is healing). *Images courtesy of Zhongli Luo's laboratory.*

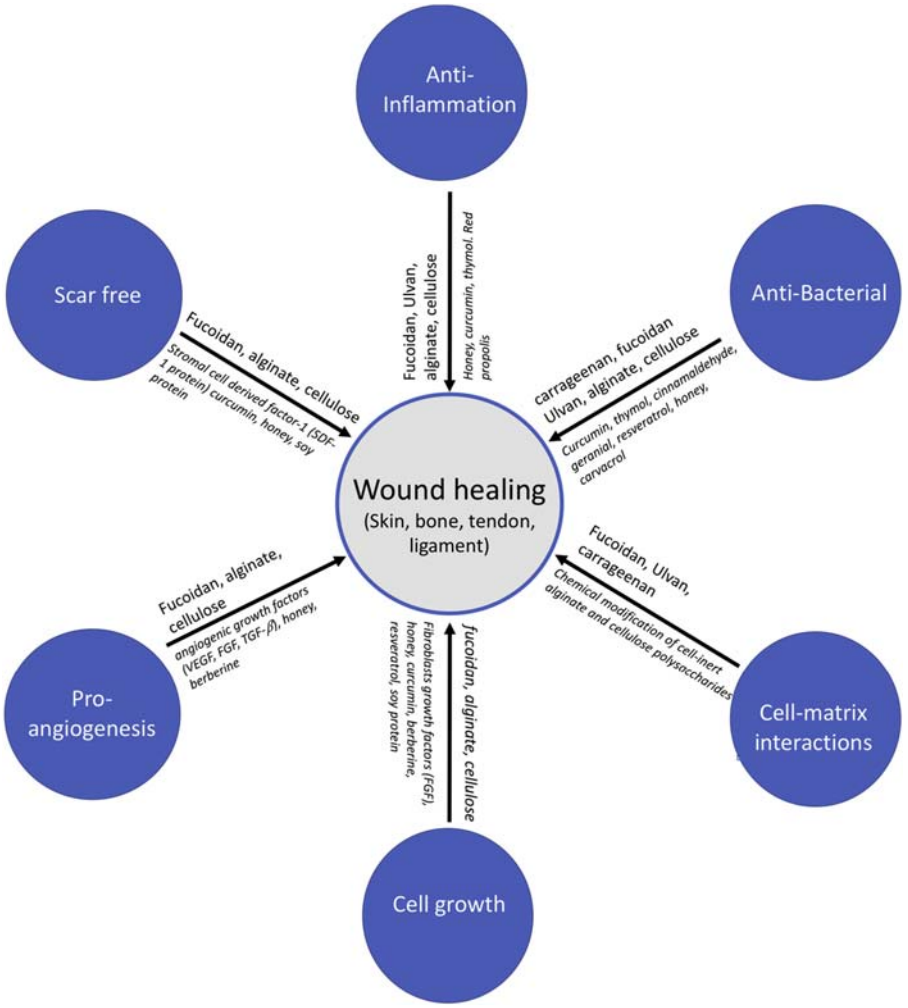
amphiphile gels were reported to promote angiogenesis, reepithelialization, and inflammatory response in streptozotocin-induced diabetic mice [164]. Multidomain peptide hydrogels, which are thixotropic and syringe deliverable, were reported to undergo rapid cell infiltration, angiogenesis, neurogenesis, and hair follicle regeneration in vivo in diabetic mice [165].

5. Nanobiomaterials and natural molecules to enhance biological performance

The wound healing cascade involves an interplay of a multitude of cell lines triggered at different phases of the healing process, i.e., homeostasis, inflammation, proliferation, and remodeling of the common tissue types. The hallmark of the proliferative phase is the formation of vascularized granulation tissue composed of collagen, glycosaminoglycans (GAGs), proteoglycans (PGs), and fibronectin produced primarily by fibroblasts. Glycosaminoglycans are common constituents of cell surfaces and the ECM, among which nonsulfated hyaluronan (HA) and sulfated chondroitin (CS) are predominant in skin and bone, respectively. They are known to modulate the activities of proteins such as cytokines, chemokines, growth factors, enzymes, and adhesion molecules and thus regulate migration, adhesion, proliferation, and differentiation of skin and bone progenitor cells [166,167]. Seaweed-derived sulfated polysaccharides with very distinct structures have been shown to exhibit similar chemical and biological properties to mammalian GAGs such as heparin/heparan sulfate and chondroitin sulfate [167,168]. The degree and pattern of sulfation have been reported to induce specific ligand−receptor interactions, which modulate antibacterial and antiinflammatory properties, the extent of growth factor-specific binding, and cell-specific behaviors [167,169], as shown in Scheme 8.8.

Fucoidan, carrageenans, and ulvans exhibit strong antibacterial activity. Fucoidan is effective against various bacterial pathogens, including *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, and *Salmonella typhi* among many others, owing to their ability to adhere to the bacterial cell surface [170−172]. Both fucoidans and ulvans possess antiinflammatory properties. Fucoidan has been found to interact with endocytic scavenger receptors on the surface of macrophages and neutrophils and inhibits selectins, enzymes (heparinase, elastase, and metalloprotease), and release of NO, COX-2, and iNOS genes and proinflammatory cytokines (TNF-α, IL-1b, and IL-6) [173,174]. Ulvan as well as high mannuronic alginate induced secretion of anti-inflammatory cytokines such as the IL-10 impeding release of proinflammatory cytokines [175−177]. MCC and pear-derived cellulose have also been shown to suppress inflammation via induction of ZEp36 gene expression and inactivation of myeloperoxidase-induced inflammation cells and nuclear factor κappa B (NF-kB) [178,179].

Carrageenans are known for their antiproliferative and antitumor properties inhibiting growth factor binding to their specific receptors in a tumor environment [180−182]. On the contrary, in chronic wounds characterized by ECM and growth factor degradation, sulfated polysaccharides act as attractive scaffolds for effective and sustained delivery of growth factors [183]. Fucoidan is one of the GAG-resembling sulfated polysaccharides


Anti-Inflammation
Fucoidan, Ulvan, alginate, cellulose
Honey, curcumin, thymol, Red propolis
Scar free
Fucoidan, alginate, cellulose
Stromal cell derived factor-1 (SDF-1 protein) curcumin, honey, soy protein
Anti-Bacterial
carrageenan, fucoidan Ulvan, alginate, cellulose
Curcumin, thymol, cinnamaldehyde, geranial, resveratrol, honey, carvacrol
Wound healing
(Skin, bone, tendon, ligament)
Fucoidan, alginate, cellulose
angiogenic growth factors (VEGF, FGF, TGF-β), honey, berberine
Pro-angiogenesis
Fucoidan, Ulvan, carrageenan
Chemical modification of cell-inert alginate and cellulose polysaccharides
Cell-matrix interactions
Fibroblasts growth factors (FGF), honey, curcumin, berberine, resveratrol, soy protein
fucoidan, alginate, cellulose
Cell growth

Scheme 8.8
Polysaccharides and their biological targets in wound healing.

widely investigated for its ability to bind with, stabilize and maintain the biological activities of growth factors such as basic fibroblast growth factors (bFGF), transforming growth factor-beta1 (TGF-beta1), and vascular endothelial growth factor (VEGF) overcoming their high diffusibility and short half-life time [184–186]. Fucoidan coupled with angiogenic growth factors, VEGF and FGF, stimulated proliferation of endothelial progenitor cells and improved in vivo vascularization essential for cell growth [187–189]. Earlier studies by a group of researchers showed enhanced proliferation of dermal fibroblasts and deposition of ECM protected from enzymatic proteolysis in the presence of fucoidan. Fucoidan decreased in vitro gelatinase A (MMP-2) and stromelysin 1 (MMP-3)

secretion by human dermal fibroblasts and leukocyte esterase activity while increasing the association of MMPs with their specific inhibitors TIMP-1 [190]. Both osteoconductive and osteoinductive properties of fucoidan enhancing proliferation and differentiation of osteoblasts as well as mesenchymal stem cells have been reported [191–193]. Kim et al. showed that fucoidan promoted proliferation and osteogenic differentiation of human alveolar bone marrow–derived mesenchymal stem cell (hABM-MSC) through BMP2-Smad 1/5/8 signaling pathway by activating extracellular-related kinase, ERK, and c-Jun N-terminal kinase (JNK) [194].

Sulfation of cell-inert polysaccharides such as cellulose and alginate induces heparin-like bioactivity. Regioselective sulfated cellulose promoted concentration-dependent 3T3 fibroblast proliferation with or without FGF-2 and stimulated BMP-2-induced osteogenic differentiation of mouse myoblast C2C12 cells to a larger extent than heparin [195–197]. Both alginate and alginate sulfate have been extensively studied as 3D scaffolds for controlled and sustained delivery of angiogenic factors including VEGF, bFGF, FGF-2, and HGF to promote in vivo vascularization in the skin and bone [198–202]. However, unmodified alginate hydrogels are unable to provide predictable and controllable patterns of proteins or growth factor release autonomously [200].

Natural molecules have been coupled with biomaterials in scaffolds to act at different stages of the wound healing process. These molecules have been carefully selected based on their reported mechanisms of action. For instance, a wide variety of natural extracts such as honey, curcumin, thymol, cinnamaldehyde, and resveratrol among many others have shown high antibacterial properties. Several mechanisms of action include disruption of bacterial cell membrane increasing their permeability, decrease in cytoplasmic pH level, their ability to bind with Filamenting temperature-sensitive mutant Z (Ftsz) protein inhibiting bacterial proliferation and inducing DNA damage response (also known as SOS response) have been reported. The antiinflammatory response of curcumin, thymol, and honey hinders leukocyte migration and recruitment of proinflammation cytokines and chemokines (cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), TNF-α, and IL-1β), which inhibits activation of nuclear factor kappa B(NF-κB) and promotes expression of antiinflammatory TGF-beta [203–208]. Table 8.4 summarizes the list of natural molecules added to the aforementioned polysaccharide-based scaffolds to improve their bioperformance in terms of inflammation, bacterial infection, proliferation, and scarring.

6. Commercially available wound healing scaffolds

Several polymeric wound healing scaffolds are currently used in the clinic for skin tissue regeneration to treat chronic wounds (Table 8.5). Very interestingly, it is important to note that collagen, hyaluronic acid, cellulose, and calcium alginate are the most successful

Table 8.4: The biological effect of natural molecules added to polysaccharide-based scaffolds.

Biomaterials	Tissue	Natural molecule	Bioperformance
Inflammation			
Bacterial cellulose [209]	Skin	Extract from red propolis	• Promote leukocyte recruitment evidenced by the high myeloperoxidase activity level and increase in proinflammatory cytokine TNF level • Accelerate wound closure by decreasing proinflammatory IL-1 level and increasing antiinflammatory TGF level associated with high concentrations of formononetin in red propolis Reduced IL-1 inhibits activation of nuclear factor kappa B (NF-κB)
Bacterial infection			
Bacterial cellulose/gelatin [208]	Skin	Curcumin	• Increase zone of inhibition against *Escherichia coli* and *Staphylococcus aureus* • High loading content and sustained release of curcumin with an increasing amount of bacterial cellulose due to its hydrophobic backbone
Cellulose [210]		Thymol	• Increase zone of inhibition against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* • Improve wound healing process by accelerating wound closure, granulation tissue, and ECM formation and reepithelialization in vivo
Alginate [211]	In vitro studies with human keratinocytes	Resveratrol and curcumin	• Increase zone of inhibition in *Staphylococcus aureus* at both 150 and 300 μg/mL of resveratrol and curcumin • 150 μg/mL of curcumin showed faster scratch closure in vitro in a confluent monolayer of keratinocytes
Alginate [212]	Skin	Honey	• Reduce viable colony counts of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* at 2% and 4% honey Glucose oxidase in honey catalyzes the conversion of glucose to D-gluconic acid and H_2O_2 as a by-product. Myeloperoxidase in honey then converts the H_2O_2 by-product to hypochlorous acid (HOCL), interfering with base pairing in the DNA of bacteria

Continued

Table 8.4: The biological effect of natural molecules added to polysaccharide-based scaffolds.—cont'd

Biomaterials	Tissue	Natural molecule	Bioperformance
Carboxymethylcellulose [213]		Chestnut honey	• An increase in colony growth at 6% and 10% honey was attributed to a rise in the total amount of carbohydrates contributing to bacterial growth • High inhibition zone against *Staphylococcus aureus* and *Escherichia coli* attributed to high methylglyoxal (MGO) level responsible for nonperoxide antibacterial activity • Early rise in neutrophils in vivo • Accelerate wound closure, granulation tissue formation, and dermal repair
Bacterial cellulose [214]	Bone	Essential oils; thyme, eucalyptus, and clove	• Eucalyptus oil displayed the lowest cytotoxicity against fibroblast and osteoblast cells • Essential oils were effective in eliminating bacterial infections and biofilm on hydroxyapatite • Clove oil offered the highest elimination ability toward *Staphylococcal* while thyme oil against pseudomonal biofilm • Eucalyptus oil was found more effective in terms of cytotoxicity and bacterial as well biofilm inhibition
Proliferation			
Alginate [215,216]	In vitro studies with human keratinocytes HaCaT and fibroblast 3T3	Honey	• Improve cell viability and proliferation of 3T3 and HaCaT • Higher expression of collagen I and III in 3T3 and E cadherin in HaCaT • Improve cell–matrix interactions
Bacterial cellulose/ gelatin [208]	In vitro studies with NIH 3T3 fibroblast	Curcumin	• Accelerate proliferation and migration of NIH 3T3 at high loading content
Cellulose acetate/ gelatin [217]	Skin	Berberine	• Increase proliferation of L929 fibroblasts in vitro • Promote epidermal proliferation and reepithelialization, collagen synthesis, and angiogenesis in vivo
Carboxymethyl cellulose [218]		Resveratrol	• Enhance epithelialization and facilitate skin appendages in vivo • Resveratrol nanoparticles promote cell internalization and accelerate cell proliferation

Continued

Table 8.4: The biological effect of natural molecules added to polysaccharide-based scaffolds.—cont'd

Biomaterials	Tissue	Natural molecule	Bioperformance
Cellulose [57]		Soy protein	• Increase integrin expression accelerating cell migration, proliferation, and production of ECM proteins in vitro
Bacterial cellulose [219]	Bone	Fisetin	• The effect of phytoestrogen in fisetin is similar to estrogen in binding to estrogen receptors and activating related signaling pathways • Act as a natural osteogenic inducer and promotes osteogenic differentiation • Support bone marrow stem cell adhesion, proliferation, and bone-specific matrix biosynthesis
Cellulose acetate [220]		Resveratrol	• Promote viability and proliferation of preosteoblastic cells and MC3T3-E1 cells • Increase alkaline phosphatase activity and extracellular matrix mineralization
Preventing scar formation			
Alginate [212]	Skin	Honey	• Promote tissue regeneration instead of contraction indicated by thinner epithelial thickness with minimum scar length
Cellulose [57]		Soy protein	• Accelerate in vivo wound closure by promoting reepithelization, epidermal thinning with a reduction in scar size
Oxidized cellulose—polyvinyl alcohol [221]		Curcumin	• High expression of fibronectin protein and E-cadherin expression closer to normal skin • Accelerate wound closure by promoting thick wavy collagen fiber organization without scar formation

biomaterials used in these scaffolds. They are highly bioactive to promote cell growth, highly absorbent to remove exudates and can contain antibacterial agents as well as other active agents such as honey.

Biomaterials have very few current clinical applications for bone tissue regeneration due to the specific requirements of highly porous material with robust mechanical properties [222–224]. The most common materials in clinical use are metal-based, calcium phosphates, or synthetic polymers such as polylactide. However, the advent of 3D printing is now accelerating the application of more bioactive materials such as chitosan, cellulose, and hyaluronic acid in this area [225].

Table 8.5: Commercially available biomaterials-based scaffolds for skin tissue regeneration.

Commercial name	Scaffold type	Clinical outcome
Integra	Cross-linked bovine collagen and chondroitin 6-sulfate with a silicone membrane	Biodegradable matrix provides a scaffold for cellular invasion and capillary growth
Promogran	Freeze-dried composite of 55% collagen and 45% oxidized regenerated cellulose	The composite matrix absorbs wound exudate to form a biodegradable gel Provide a scaffold for cellular migration
Aliginate-based: Tegagen, Algisite, and Algi-Fiber	Dressings of calcium alginate fibers Form gelatinous mass upon contact with wound exudate	Extremely absorbent (10×) and controls mild hemorrhages
Talymed	Shortened fibers of *N*-acetyl glucosamine isolated from microalgae	Material interacts with fibroblasts and endothelial cells to stimulate cell migration
Hyalomatrix	Nonwoven pad of benzyl ester of hyaluronic acid and a semipermeable silicone membrane	Biodegradable scaffold for cellular invasion and capillary growth Contain a semipermeable silicone membrane to prevent water loss

Commercial scaffolds for tendon and ligament repair are mainly fabricated using porcine and bovine dermis, and synthetic polymers such as polyurethane [226]. The new trend is to be able to use biomaterials as a coating on synthetic polymers to improve adhesion and bone attachment [227]. Scaffolds for ligament repair currently called medical textiles are using this approach successfully in clinical or nonclinical trials (Table 8.6).

Table 8.6: Some medical textile scaffolds for ligament repair.

Scaffold	Biomaterial	Clinical implications
BEAR (Bridge-Enhanced ACL Repair) scaffold [228]	Uses stitches and a bridging bioactive scaffold (a sponge injected with the patient's blood) to stimulate healing of the torn ACL	• No graft harvest of patient's tendon • The remaining ACL tissue is preserved • The BEAR Implant is an investigational device and is only available in FDA-approved clinical trials
BIOFIBER CM Collagen-coated absorbable scaffold [229]	Collagen on poly-4-hydroxybutyrate	-
BioBrace implant [230]	Biocomposite scaffold A highly porous collagen matrix, embedded with bioresorbable polymer microfilaments, to provide an open 3-D biologic scaffold with strength	• Intended for the reinforcement of soft tissue where weakness exists • BioBrace is not yet FDA cleared for commercial sale or clinical use in the United States

7. Conclusion and future perspectives in wound tissue regeneration

The healing process is a complex one occurring in three phases, such as management of the inflammatory process, cell proliferation, and ECM remodeling. In this chapter, we have discussed the efficacy of some nanobiomaterials used as scaffolds—cellulose-based, seaweed polysaccharide-based, sucrose-based, and peptide hydrogels—in enhancing wound healing and promoting tissue regeneration over a repair that is preventing the formation of scars. The nanobiomaterials probably play an important role in modulating the immune response and collagen production, thus promoting scarless regeneration. The applicability of such scaffolds to different types of the wound has yet to be proven in the clinic.

Burn wounds remain a challenge, particularly for third and fourth burn degree and their associated complications such as infections and damage to bones, muscles, and tendons. In addition, deep dermal and full-thickness burn injuries require operative intervention [231]. The use of injectable hydrogel scaffolds for burn wounds is a promising avenue, as they can not only cater for heterogeneous wound morphologies and cavity wounds but also provide a moist environment ensuring a soothing effect for patients [232].

Bone regeneration using nanobiomaterials scaffolds has not yet reached the same level of clinical application as for skin regeneration. The regeneration of critical-sized bone defects is very challenging, as the scaffolds have to act as temporary support for bone tissue growth while exhibiting mechanical integration via proper load transfer to host tissue in the proximity of the scaffold and in parallel allow for vascularization and tissue regeneration within its structure. Porosity, pore size and pore shape, degradation rate, and elastic modulus are important parameters for these scaffolds. Thus scaffold geometry, its mechanical property, and biological processes should work in unison making the design of the scaffold a daunting task [233]. Nowadays, computer-aided engineering (CAE) tools are solving these challenges in the proper design of scaffold architectures. However, bone regeneration scaffolds are believed to be able to bring an important contribution to addressing the problem of osteoporosis [234]. The latter is among the most prevailing age-associated diseases characterized by the deterioration of bone strength with an increase in fragility fractures. Scaffolds can thus be used as a support for the existing weakened bone on which new bone can grow and also for local delivery of biologics such as BMPs and MSCs.

Collagen is the major constituent of ligaments and tendons, which are themselves constituted of 70% water with structures that include blood vessels, nerves, and lymphatic vessels, and they perform the task of linking bone to muscle and moving the body. There is an immense clinical need for the development of readily available, off-the-shelf, mechanically strong scaffolds for these two tissues. Immobilization casts and movement

restricting splints and braces requiring several weeks of rehabilitation to achieve minimal functional recovery are the most commonly used repair techniques. Synthetic implants would have to not only fulfill a mechanical function of tendons and ligaments but also support the growth of collagen tissue, without compromising the body's biological response. Given the complexity of the human tissue, a single biomaterial may not fulfill the requirements for restoration of the original tissue after a wound. The use of biomaterial blends opens up a vast horizon of possibilities in tissue engineering mimicking the components of the human ECM where each component has a well-orchestrated role to play in restoration and repair.

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Further reading

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CHAPTER 9

Polymeric bionanomaterials for diabetes applications

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1. Introduction

Diabetes mellitus (DM) affects the lives of about half a billion individuals worldwide [1]. It is a chronic metabolic illness that is divided into two main classes, i.e., type 1 diabetes (T1D) and type 2 diabetes (T2D) [2]. T1D originates from autoimmunity due to the immune system T and B cells. The β-cells that are located in the pancreas and have the role of secreting insulin are targeted and destroyed by the T and B cells, leading to the total inability to provide insulin [3]. T2D is related to a lifestyle that contains very little or no physical activity (sedentary lifestyle), which results in the resistance of cells to respond to insulin. In diabetes conditions, prolonged hyperglycemia is a common symptom, while this may lead to more serious complications and eventual death. Therefore, therapies that involve the administration of insulin are very crucial to manage and treat diabetes, while patients are customarily obliged to receive multiple injections daily. This type of administration has several disadvantages and is often accompanied by poor compliance of the patient. In addition, such insulin therapies are not effective in diminishing the fluctuations in the blood glucose level (hypo/hyperglycemia), and they fail to sustain blood glucose levels similar to the ones of healthy individuals. An ideal treatment would include an antidiabetic drug delivery system that is responsive to blood glucose levels and is able to release the drug at the proper dosage.

Polymer science has naturally found application in the delivery of antidiabetic drugs as it can provide formulations that can be manipulated at the nanolevel in terms of both characteristic sizes and interactions between nanosized objects. The size and surface properties of a polymeric nanoparticle (NP) determine its ability to cross biological

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barriers and deliver biologically active compounds to the desired sites [4]. Additionally, proper design of polymeric NPs is required, so that the encapsulated drug release is prolonged, its bioavailability is high, and its efficacy is not compromised.

Polymeric nanostructures offer great possibilities in tissue engineering and drug delivery. Typical examples are the nanovesicles and nanocarriers of gene and protein/peptide drugs [5,6], enzymatic nanoreactors, and (bio)responsive surfaces [7]. Synthetic macromolecules come in a wide variety of architectures and chemical compositions, depending on the topology of their polymeric chains and choice of building blocks (monomers). Examples include block copolymers with amphiphilic character and polyelectrolytes that contain ionizable groups that dissociate in water. Self-assembly in amphiphilic block copolymers in aqueous media leads to the formation of core—shell micelles with nanodimensions that can solubilize hydrophobic drugs in the interior of their hydrophobic core. Simultaneously, their hydrophilic shell allows them to circulate in aqueous media and enter the microenvironment of tissues and cells [8]. Polyelectrolyte-based macromolecules, e.g., amphiphilic block polyelectrolytes and hydrophobically modified polyelectrolytes, can interact with charged entities in solution such as oppositely charged macromolecules, to produce nanoparticulate complexes [9], including proteins for applications in protein delivery and separation [10]. There are unlimited possibilities to synthesize functional nanoarchitectures using the conjugation between block copolymers and proteins, given the chemical and architectural diversity of synthetic polymers, which is due to the progress of polymer synthesis. The correct choice of the corresponding proteins and the interaction mechanisms between the components result in the formation of a plethora of innovative nanostructures with a wide range of structural properties and functionalities. These nanostructures can be easily adapted to specific applications in the fields of nanomedicine.

Biopolymers, e.g., polysaccharides, are macromolecules that very often are hydrophilic and contain chargeable units. Polysaccharides are polymers that are found in nature as structural building blocks or store solar energy in the form of sugar for fuel cells. They are a sustainable source of fully biodegradable nature-provided polymeric materials. They are used in applications, such as the controlled release of agrochemicals in soils [11], drug delivery in pharmaceutics [12], and in the food industry [13]. Delivery of bioactive components by nanoformulations—like the ones based on polysaccharides—is very often preferred, as it promotes high delivery efficiency (due to high surface-to-volume ratio), while bioactivity and acceptability of the beneficial components are increased in the aqueous environment of the human body.

A very common DM disorder is a patient's problematic wound restoration. In many cases, chronic traumas and skin disruptions occur. The inefficient control of blood glucose levels is the main reason that prevents the normal healing of such a wound. Apoptosis in the wound bed in DM conditions is caused by the low plasma fibronectin, chemokines, and

proangiogenic growth factors, which lead to a delay of the inflammatory response [14]. Biomaterials from synthetic and/or biological polymers are very often used to prepare hydrogels for application in wounds, to deliver insulin, growth factors, and even cells, hence facilitating a healthy wound closure. Polymer hydrogels can accommodate large amounts of aqueous media, e.g., biological fluids, which is the physical environment for proteins, cells, and tissues. They are hierarchically structured at the nano- and microlevel and therefore can interact with nanoformulated drugs and proteins (nanoscale) and also cells (microscale), providing mechanically robust scaffolds to support the formation and function of cells and tissues [15].

In this chapter, the current trends and advances in the treatment of DM based on polymeric bionanomaterials are presented. The main discussion is divided into two subsections, one being about the use of NPs in the treatment of DM and the other being about the use of hydrogels, mostly for the treatment of wounds. Both these broad categories are very important for current polymer science, as they are used in biomedical and biotechnological applications and take advantage of the organization of soft matter at the nano- and microlength scales. As DM is up to now a disease with no known or well-established cure, polymeric NPs are very promising in regulating blood glucose levels in a stimuli-responsive manner, while polymeric hydrogels can provide healing to abnormal wound ulcers that appear as a main symptom of the illness. The discussion demonstrates the versatility of polymeric materials to form nanostructures that are biocompatible and nontoxic and can deliver bioactive substances that would otherwise be difficult to administer, e.g., with poor solubilization and bioavailability.

2. Delivery of antidiabetic medicines using nanoparticles

2.1 Chitosan-based nanoparticles

Chitosan (CHT) is a very common polysaccharide employed for insulin loading, transport, and release at the nanoscale. It is the most preferred choice due to its unique characteristics, such as low toxicity, biodegradability, and abundance in nature. CHT is a positively charged polyelectrolyte that can efficiently adhere to soft tissues and has desirable kinetics and biodistribution when it comes to drug delivery or release [16]. CHT chemical structure, crystallinity, deacetylation degree (DD), and molecular weight affect its physicochemical properties, such as insolubility−solubility transition below pH 6, viscosity, and conditions of degradation. CHT has been combined with other natural polymers or synthetic ones to produce copolymers. In several cases, CHT has been modified to change the insolubility−solubility transition point to higher pH values or was used as an additive to functionalize polymeric NPs. CHT has been combined with proteins (DZ13SCR), inorganic NPs (PSi), or pharmaceutical NPs (nanocurcumin) for applications, such as protein delivery and wound healing applications.

Zhou et al. [17] combined CHT with the synthetic polymer polyacrylic acid−cysteine-6−mercapto-nicotinic acid (PC6). CHT NPs were prepared by electrostatic interaction between the positive CHT and the negative insulin, while tripolyphosphate (TPP) was used as a cross-linker. Subsequently, the CHT/insulin NPs were stirred together with PC6 in solution for about 1 hour. Because of the electrostatic interaction between negative PC6 and positive CHT/insulin NPs, a composite product was finally obtained. For the characterization of the resulting system, dynamic light scattering (DLS), transmission electron microscopy (TEM), fluorescence spectroscopy, and high-performance liquid chromatography (HPLC) were employed. While most CHT NPs were disassembled at pH between 5.5 and 6.8, the PC6/CHT NPs were more stable in the entire pH range, according to the obtained TEM images. The produced NPs were able to penetrate the mucus successfully, and they enhanced the transport of insulin through the tight junctions of the epithelial cells, i.e., paracellular.

A similar system of poly(ethylene glycol) (PEG)−grafted CHT NPs for nasal absorption of insulin was explored [18]. In this chapter, the preparation of PEG-g-CHT assemblies was based on the ionic gelation of CHT with TPP anions. Either NPs or large aggregates were formed, whereas insulin was loaded by adding it to the solution under magnetic stirring. Characterization of the system was achieved by TEM, photocorrelation spectroscopy (PCS), Doppler anemometry, and X-ray photoelectron spectroscopy (XPS). The researchers reported that insulin followed an initial rapid diffusion from the NPs into the release medium and a subsequent slow release due to swelling or degradation of the polymer networks. A maximum of 84% of the insulin release was achieved in that work. PEG-g-CHT NPs were regarded as more efficient drug carriers of insulin through the nasal mucosa in comparison with their counterparts where no NPs were formed. Thiolated CHT NPs were synthesized by a reaction between the polysaccharide and pentaerythritol tetrakis (3-mercapto-propionate) for the delivery of insulin by oral administration [19]. Tests on diabetic rats showed that biodistribution and bioavailability of insulin were sustained because of the interaction of the NPs with the intestinal mucosa.

Sheng et al. [20] formulated an *N*-trimethyl chitosan chloride (TMC) coating of poly (lactic-co-glycolic acid) (PLGA) NPs, in the core of which insulin had been encapsulated. The formulation of the NPs was achieved by a double-emulsion technique, and ultrasound sonication or magnetic stirring was employed to mix the materials. The researchers were interested in combining the controlled-release property of PLGA NPs with the mucoadhesive and permeation, enhancing the capacity of modified CHT. It is discussed that three barriers need to be overcome in the case of insulin's oral bioavailability: the enzyme barrier in the gastrointestinal tract (GIT), the mucus barrier, and finally the epithelial cell barrier in the intestine. In addition, tight junctions further hinder the transport of insulin. The NPs' structure, size, and polydispersity were studied by TEM, DLS, and ultraperformance liquid chromatography (UPLC), while the in vitro release of

the enclosed drug was also tested. It was calculated that less than 10% of the drug was released in the enzyme-free test tubes and approximately 30% of the drug in the enzyme-containing tubes was released during the first 1 h, followed by a more sustained release over the next 5 h, in both cases. A final 30%−50% of the insulin retention inside the NPs' core was reported, which was indicative of the drug delivery system's (DDS) resistance against enzymatic degradation. The TMC-PLGA system seems to be a promising one, as the NPs were able to firmly attach themselves to the lower part of the small intestine, extending the release time of insulin at the target area.

Furthermore, Vijayan et al. [21] synthesized another CHT composite system for transdermal delivery of antidiabetic drugs is explored. The work was focused on the formulation of CHT, polylactic acid (PLA), and polycarpolactone (PCL) composite NPs, encapsulating repaglinide, an alternative medicine against diabetes. The bionanosystem was prepared using the solvent-extraction method, and the produced NPs' sizes were between 108.6 ± 3.4 nm and 220.6 ± 1.2 nm, as obtained by scanning electron microscopy (SEM) and DLS. Fourier transform infrared spectroscopy (FT-IR) was also used as a characterization technique. The release profile of repaglinide was low over a significant amount of time due to the formation of a compact wall around the drug by the biodegradable polymer. By the end of the 24 h period, the percentage of the released drug was between 73% and 87%. This study concluded that transdermal delivery of repaglinide is preferred over oral one, making the drug more effective in reducing glucose levels in the plasma.

Araujo et al. [22] prepared and studied another interesting bionanosystem for oral delivery of two diabetes-related drugs: GLP-1 (glucagon-like peptide-1) and iDPP4. GLP-1 is one of the most promising therapeutic molecules for T2DM therapy but has a very short half-life of fewer than 2 minutes due to the DPP4 enzyme. However, in the presence of iDPP4, the activity of the enzyme responsible for degrading GLP-1 was significantly reduced, which justified the reason that a combination of the two drug components was chosen. The system's assembly was achieved by the droplet microfluidics technique, and it consists of PLGA NPs, which can provide a protective, stable, and biocompatible environment to the encapsulated peptides and proteins. These NPs were functionalized with CHT and a cell-penetrating peptide (CPP); hence the resulting double-DDS showed strong interactions with intestinal cells in vitro. Once the NPs were functionalized, they were encapsulated within an enteric polymer—hydroxypropylmethylcellulose acetyl succinate (HPMC-AS)—making them pH sensitive and active only under the desired intestinal conditions. NPs had spherical shapes and sizes in the order of 100 nm (Fig. 9.1). Their physicochemical characterization included DLS and HPLC, whereas their biocompatibility and effectiveness were investigated by in vivo tests in rat models with induced T2DM. This novel strategy to simultaneously deliver two drugs in the nanoscale was deemed successful because 4 h after administration, blood glucose levels were dropped by 44%.

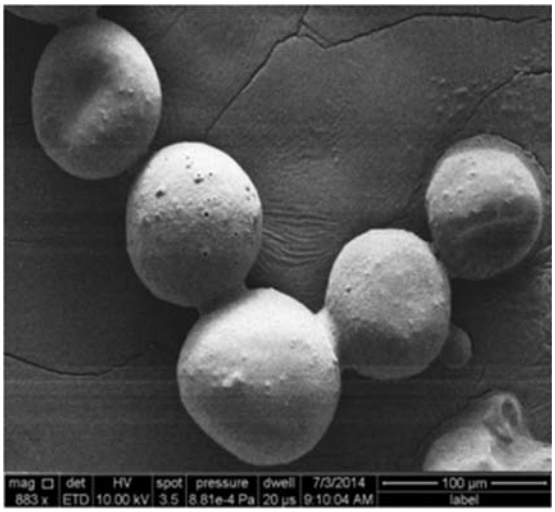

Figure 9.1

SEM image of NPs modified by CHT-CPP and encapsulated in the HPMC-AS polymer. *Reproduced from F. Araújo, N. Shrestha, M.J. Gomes, B. Herranz-Blanco, D. Liu, J.J. Hirvonen, P.L. Granja, H.A. B. Santos, B. Sarmento, In vivo dual-delivery of glucagon like peptide-1 (GLP-1) and dipeptidyl peptidase-4 (DPP4) inhibitor through composites prepared by microfluidics for diabetes therapy. Nanoscale 8(20) (2016) 10706—10713 with permission.*

Another system for oral administration of the previous two drugs involved mesoporous silicon NPs—which were used for easy surface modification and drug loading in mild conditions- and CHT, which was combined to add an extra mucoadhesive property [23]. A single-step process called aerosol flow reaction (AFR) was employed for the polymer coating of the PSi NPs. This technology avoids the use of toxic organic solvents while temperature could be controlled easily during the reaction/coating process. GLP-1 was loaded to the NPs using an immersion technique, whereas the DPP4 inhibitor was incorporated into the CHT coating matrix. The system was characterized physicochemically by DLS and TEM and exhibited strong adhesion to the intestinal epithelia of rats and a successful decrease in blood glucose levels.

A natural substance, curcumin, which is derived from the turmeric of an herb called *Curcuma longa* [24], has been encapsulated in various polymeric NPs for the treatment of DM. Curcumin-loaded CHT NPs were prepared through ionic cross-linking [25]. The solution was at room temperature and kept under magnetic stirring for 24 h. Physicochemical characterization was achieved by TEM and DLS, and the release of curcumin was estimated by measuring the fluorescence absorbance of the dispersion. Curcumin's loading capacity was 35.1% (mass of loaded drug/mass of NPs), whereas the drug was completely released after 72 h. The NPs were considered as a highly effective way to accelerate the healing of diabetic wounds. A slightly different system was proposed

for the CHT-ZnO-nanocurcumin NPs [24]. Preparation of the ZnO NPs was made by pouring a curcumin dispersion into a zinc acetate solution. Mixing the two media required an increase in temperature to 40−50°C, then the NPs were dried, and curcumin was washed off. Subsequently, ZnO NPs were dispersed in a solution of CHT NPs, and the dispersion of nanocurcumin in ethanol was added last, to be stirred for 90 min at room temperature with the first solution. Afterward, the centrifuged and dried complex NPs were characterized by differential scanning calorimetry (DSC), FT-IR, and HPLC, and their size and toxicity were evaluated. Regular administration of the NPs over almost a month resulted in a serious reduction of blood glucose levels, while zero cytotoxicity, antioxidant activity, and better solubility of curcumin were also observed.

In another related study [26], CHT was again the hydrophilic carrier of curcumin NPs. The preparation procedure took 6 h, where the stirring of CHT NPs, curcumin NPs, and TPP and the encapsulation of curcumin in the CHT NPs were done instantaneously. Then the solution was centrifuged, and the formed NPs were observed through electron microscopy, both SEM and TEM (Fig. 9.2). Average particle size of 74 nm was found by TEM. The main result of this study was that nanocurcumin contribution to translocate GLUT-4—an insulin-regulated transporter found in skeletal and cardiac tissue—was superior to the one of plain curcumin. The authors also claimed that the produced NPs can potentially

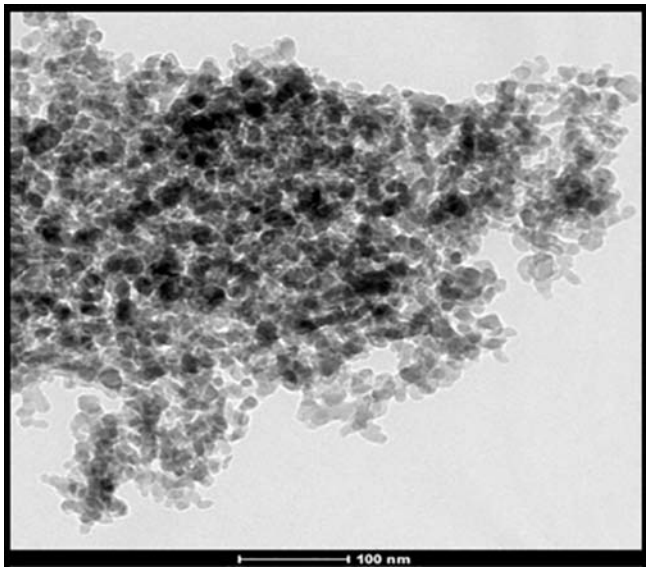

Figure 9.2
TEM image of CHT-encapsulated nanocurcumin. *Reprinted from P. Chauhan, A.K. Tamrakar, S. Mahajan, G.B.K.S. Prasad, Chitosan encapsulated nanocurcumin induces GLUT-4 translocation and exhibits enhanced anti-hyperglycemic function. Life Sci. 213 (2018) 226−235 with permission.*

improve glucose disposal in skeletal muscles. Finally, according to Boarescu et al. [27], curcumin NPs act as antioxidant and antiinflammatory biosystems and reduce or prevent acute myocardial infarction in diabetic rats.

Combinations of CHT with proteins have been commonplace in recent literature regarding the oral delivery of insulin. In one case, a mucin/CHT complex system was developed [28], where insulin was encapsulated and transferred to the desired areas. Mucin is a polyanion and is, therefore, a suitable candidate to electrostatically bond with CHT, making the final product mucoadhesive and facilitating drug protection and absorption through the intestinal mucus. The production of nanocomposites involved the first incubation inside a weak alkaline solution of dopamine and a second incubation with additives, such as ligands. The modified NPs could interact with cells, exhibiting no toxicity and no residual bioactivity of the dopamine molecules. Nonetheless, researchers point out that a main disadvantage of the CHT-based NPs is the easy protonation of CHT, when in an acidic environment, which results in degradation of the bionanosystem and eventual release of insulin. Mucin is a polysaccharide that has been proposed to counteract this drawback. The final composite NPs were characterized by DSC, FT-IR, SEM, and DLS, and toxicity/stability studies were also performed to test their safety. In vivo and in vitro evaluations depicted a hypoglycemic effect in diabetic rats after the peroral administration of the formulation, which was more profound than this of an insulin solution.

A different protein that has been paired with CHT is DZ13SCR [29]. Again, the two ingredients of the composite NPs are oppositely charged, and they manage to hold insulin inside their matrix. The morphology, drug-release profile, glucose regulation, and oral absorption mechanism were characterized using HPLC and SEM. As in the previous case study, the protein DZ13SCR enhanced the mucoadhesiveness of the NPs in the GIT and due to CHT, toxicity was eliminated, making the final product biocompatible and safe to use. Complex (polyelectrolyte) coacervation was the fabrication technique used to produce the DZ13SCR/CHT NPs. This is a mild method applied to encapsulate sensitive therapeutic agents into NPs, and it is preferred over others as it does not involve dangerous organic solvents, sonication, vigorous agitation, or heat. The NPs produced via this technique are reported to have a small size, appropriate surface charge, uniform distribution, spherical morphology, and colloidal stability, and they remain pH sensitive. After preparation, the NPs were freeze-dried to guarantee their stability and bioactivity upon storage. However, due to the mechanical stresses that are involved in a lyophilization process and not to jeopardize degradation or particle aggregation, a cryoprotectant called mannitol (7% w/v) was selected and utilized.

CHT has been combined with lecithin to encapsulate and orally deliver insulin [30]. For its preparation, CHT and insulin were added in an HCl solution, until a pH of 1.3 was

reached. Then, L-arginine solution was added dropwise to restore the neutral pH, and the first solution was complete. Lecithin was added to an ethanol solution, was sonicated, dried, and finally added to a distilled water solution. This was poured inside the first solution, and they were stirred together for 5 minutes at room temperature. The bionanosystem was characterized via SEM regarding its morphology and size, while pH-related, surface tension, stability, and pharmacological tests were performed, too. It was found that lecithin liposomes enhanced the stability of insulin inside the CHT nanovesicles and the complex DDS was not absorbed easily on various tissue surfaces. Also, the hypoglycemic effect was more profound and lasted longer than in the case of subcutaneous insulin administration (i.e., under the skin injection).

Ionotropic gelation between CHT and insulin with the aid of TPP was used to deliver insulin by oral administration. NPs were prepared at two different pH values (pH 5.3 and 6.1). At pH 6.1 the NPs had higher size and lower surface charge than the ones formed at pH 5.3. A test that simulated the transit through the GIT was realized by incubating the NPs at gradually decreasing pH, adding 0.1 M HCl solution for 30 min, then raising the pH from gastric to intestinal conditions (pH 6.8−7.4), and incubating for another 30 min. The size of the NPs decreased significantly, while their zeta potential increased with an accompanying decrease of the association efficiency of insulin. At intestinal conditions, both the size and zeta potential decreased, while association efficiency was unaffected. Both kinds of NPs were successful in reducing glycemic conditions in diabetic rats after oral administration. The NPs prepared at pH 5.3 with a dose of 100 insulin units/kg were able to maintain a glucose level in the serum at values similar to prediabetic conditions. Insulin encapsulated in the CHT−insulin NPs was proved to be mainly responsible for the observed pharmacological response, in comparison with unloaded NPs and unassociated insulin in solution [31].

2.2 Nanoparticles of other naturally occurring biopolymers

All the bionanosystems presented earlier make use of CHT and its biofriendly properties in the pursuit of diabetes treatment. However, other natural polysaccharides are also employed as polymeric insulin nanocarriers. The following two paragraphs will present dextran, amylose, and amylopectin, which—just like CHT—are used either after chemical modification or in combination with another substance. Dextran is a branched homopolysaccharide of glucan, which may be industrially produced by growing cultures of the bacterium *Leuconostoc mesenteroides*, along with sucrose, an organic source of nitrogen, growth factors, minerals, and phosphate [32]. It is water soluble, biocompatible, and biodegradable and can remain stable for several years after production. Amylose and amylopectin are both polysaccharides that stem from starch, a nontoxic, inexpensive, and

biodegradable biopolymer with suitable rheological properties for drug encapsulation and release. Amylose is a straight-chain hydrophilic polymer, whereas amylopectin is a branched one and the largest of the two [33].

In the work of Volpatti et al. [34], acetylated dextran NPs are formulated for insulin, GOx, and catalase encapsulation and the delivery of the former in an injectable way. GOx converts glucose to gluconolactone, which is then hydrolyzed into gluconic acid and reduces the pH of the environment when glucose levels are high. In this low pH, the acetal groups of the modified dextran are cleaved, solubilizing the NPs and releasing the encapsulated insulin. The authors synthesized several dextran polymers with varying degrees of modification induced by acetyl cleavage, to achieve the desired drug-release kinetics. The morphology of the NPs, their size and degradation process, and the amount of induced modification were studied by TEM, DLS, and hydrogen nuclear magnetic resonance (H-NMR), respectively. Although these coformulated NPs reduce elevated blood glucose levels in diabetic mouse models and can afford a 16-h glycemic control, the authors report potential toxicity and immune response provoked by repeated administrations as open issues for future investigation. A completely different nanocomposite system of concanavalin-A (Con-A) and amylopectin has also been proposed as a carrier for insulin [35]. The preparation procedure involves the gelification of an amylopectin dispersion in a boiling water bath and the addition of a salt (NaCl) solution of the protein Con-A. Various mass ratios were tested, and through DLS, TEM, fluorescence spectroscopy, FT-IR, and circular dichroism spectroscopy (CDS), the researchers tried to identify the most promising mass ratio of the two ingredients. The particle size ranged from 100 to 300 nm, and the mass ratios are reported to affect the pH and ionic strength of the samples. FT-IR confirmed the interactions of Con-A and amylopectin, due to which the NPs were formed. A 70% encapsulation of insulin was achieved, and its release was also successful in the presence of glucose in the medium.

Zein-carboxymethylated amylose NPs have been discussed as a potential oral insulin administration method [36]. Antisolvent coprecipitation was the physical technique that was employed to prepare the zein/amylose NPs. In the beginning, low-molar-mass amylose was lyophilized and added in an ethanol solution along with NaOH (alkalization) and monochloroacetic acid (etherization). The product was neutralized, filtered, washed, and dried, to be used in different concentrations in distilled water. A protocol of heating it to 100°C and cooling it down to room temperature while stirring took place before the amylose water solution was blended with the ethanol solutions of insulin and zein (ratio 1:3). NPs started to form at a pH around 5, and they were further studied by fluorescence spectroscopy, DLS, FT-IR, X-ray diffraction (XRD), TEM, and cytotoxicity tests. The NPs were homogenous, spherical (<200 nm), and negatively charged. The interactions between zein and amylose were either hydrophilic or electrostatic, as shown in FT-IR spectra.

The complex system of zein/amylose NPs seems to work better when compared with pure zein NPs because it has doubled the efficiency to encapsulate insulin (90%) and it is nontoxic to cells.

In a later work of the same group [37], a zein-carboxymethylated amylose/CHT nanocomposite system was formulated to improve the properties of bionanomaterials even more. The new NPs' average diameter was slightly larger (310 nm), but both systems have a similar encapsulation efficiency of up to 90%. They are biocompatible too but have a stronger impact on glucose regulation than the zein-carboxymethylated amylose NPs. They have been studied by the same characterization techniques, and the same protocol was used to prepare the zein-carboxymethylated amylose NPs. For the nanocomposite preparation, CHT solutions of different concentrations in acetic acid were added dropwise to the NP solution up to equal volume. The two solutions were magnetically stirred for about an hour. The main outcome of the second study was that the new CHT-coated NPs enhanced the oral bioavailability of insulin in the targeted areas.

In this last section, we will discuss a nanocomposite system for protein delivery, comprised of GG, CS, and HA [38]. GG is transparent, resistant to heat, and not cytotoxic [39], CS is an antioxidant and not immunogenic [40], and HA is a semitransparent, elastic, photosensitive, and hydrophilic material. In this case, Haine et al. suggest gold (Au) nanorods—coated with the aforementioned polysaccharides—as suitable nanocarriers for proteins. They are activated by the photothermal effect, and they can deliver proteins—like insulin—transdermally. This new innovative technology seems highly promising, as it includes gels that are activated by lasers in the near-infrared (NIR) spectrum; hence the proteins that are carried by the nanorods can permeate the skin more easily. Testing of the complex bionanosystem concerned the protein named fluorescein isothiocyanate−modified ovalbumin (FITC-OVA). For the gel preparation, a fixed mass of GG was diluted in distilled water, and different ratios of CS and HA were added and stirred for about 5min. Then drying of the films and protein pouring onto the films' surface followed. This study was in a premature phase, and more proteins and antigens need to be tested, especially regarding their stability against NIR laser radiation, but the developed patch was transparent and protein translocation was achieved locally and noninvasively.

NPs with an average diameter of 300 nm were prepared by octa-arginine-modified alginate and were used for oral insulin delivery [41]. The modification led to superior stability in simulated gastrointestinal fluids, better controlled release, and improved intestinal uptake of insulin. In another work, alginate microgels were prepared by electrospraying and served as scaffolds for the encapsulation and protection of dextran NPs that were responsive to glucose [42]. The NPs had a rapid response to elevated glucose concentrations while they sustained the glycemic control for 22 days. Hydrogel

microparticles from polysaccharides (carboxymethyl chitosan, carboxymethyl β-cyclodextrin) that were loaded with insulin reduced the symptoms of polydipsia, polyphagia, polyuria, and weight loss in rats after long-term treatment [43].

2.3 Nanoparticles of synthetic biopolymers

In this section, NPs based on synthetic polymers, i.e., biocompatible polymers that are derived by chemical synthesis and do not originate from natural sources are presented. The multiple emulsion method has been used to prepare NPs of poly(ε-caprolactone) and the acrylic polymer Eudragit. The NPs were loaded with insulin and had a size of 350 nm, somewhat larger than their size in the case of no added insulin, which was about 330 nm. The NPs encapsulation efficiency was higher than 95% as was proved by HPLC. The glycemic profiles caused by insulin injection in diabetic rats in the form of free drug and drug-loaded NPs were similar. Nevertheless, the maximum drop in glycemia occurred 8h after subcutaneous administration for insulin-loaded NPs in comparison with administration of free insulin with 4h. Additionally, the hypoglycemic action of the encapsulated insulin was maintained for longer than 12h, whereas it was 10h for nonencapsulated insulin. Orally administered NPs led to a glycemic reduction at doses higher than 50 insulin units/kg, while aqueous solutions of insulin that were orally administered did not have any effect at any dose. The insulin-loaded NPs performance in glucose tolerance tests was satisfactory. Finally, the cationic nature of Eudragit was proposed to be responsible for the effective uptake of the NPs by the intestinal mucosa, as it was supported by fluorescence microscopy with FTIC-labeled insulin [44].

Insulin in the monomeric form can be modified by recombinant DNA technology. The B28 amino acid, normally proline, is substituted by the residue aspartic acid. This enhances the electrostatic repulsions between monomers, and consequently, the aggregation into dimers and hexamers are eliminated. The monomeric form of insulin has an enhanced rate of absorption (three times higher) in comparison with human insulin, and this results in a faster increase of its concentration in plasma and a prompt hypoglycemic response after hypodermic injection. Poly(ε-caprolactone)/Eudragit NPs—prepared by the multiple emulsion method—were applied to diabetic rats. The diabetic condition was induced by injection of streptozotocin in NaCl. Glycemic levels above 300 mg/dL after 2 weeks of treatment with streptozocin were considered as the criterion for a diabetes diagnosis. In general, the NPs were larger than the ones made with conventional insulin. Aspartic acid has a pKa lower than 3, whereas proline's pKa is at 6.8. Therefore, at physiological or mildly acidic conditions, aspartic acid remains charged and experiences a strong electrostatic attraction with Eudragit. The insulin-containing NPs were orally administered to the diabetic rats. A sustained reduction of hyperglycemia levels for longer than 8h was achieved. Modified insulin had a stronger effect than the regular one because

of the more efficient absorption of monomeric insulin in comparison with the human insulin, which is in the hexameric form. The effect on hypoglycemia was reported to be nondependent on the dose, while glucose tolerance was substantially improved [45].

Block copolymers of PEG with poly (2-aminoethyl-L-glutamate) that was grafted with poly (L-lysine) were loaded with insulin to prepare a system that could be applied to renal ischemia/reperfusion injury, associated with DM. Rats were administered free or encapsulated insulin, before being subjected to ischemia/reperfusion injury. The uptake rates of glucose from the pancreas were significantly lower in DM groups than in non-DM groups. However, administration aided by the polymeric nanocarriers increased the glucose uptake. The decreased levels of glucose transporter-4 (GULT4) mRNA in DM rats were increased by the encapsulated insulin, whereas in the case of free-form insulin the effect on GULT4 mRNA levels was weaker. Similarly, the amount of GULT4 in the cell membranes of DM rats was enhanced by the nanocarriers. Overall, the proposed nanocarrier complex system showed promising results for protection, controlled release of insulin, and eventually renal function recovery [46].

The model drug liraglutide comes from the modification of GLP-1, by attaching a fatty acid tail and an Arg34Lys substitution. These changes allow for stronger intermolecular aggregation and binding to albumin and other compounds noncovalently. The half-life of liraglutide is extended, while the drug maintains the physiological functions of GLP-1 (e.g., it stimulates insulin release and suppresses glucagon secretion). Two thermogelling triblock copolymers, with PEG as the middle block, poly(ε-caprolactone-co-glycolic acid) (PCGA) in one side and poly (lactic acid-co-glycolic acid) (PLGA) in the other—as end blocks—were used for the encapsulation and delivery of liraglutide. These polymers self-assemble into flower-like micelles in an aqueous solution at room temperature with size in the order of 30–40 nm. Loading them with the drug leads to a slight increase in their size (Fig. 9.3). The solutions experience a dramatic sol–gel transition at ~27 °C, whereas their solid-like behavior is established at physiological temperature, i.e., 37°C. The in vitro release of the drug at physiological conditions can be sustained to periods longer than 9 days, whereas in the case of commercial thermogelling polymers (Pluronic), burst release is completed within 2 days. In more detail, PCGA–b-PEG–b-PCGA has side blocks with higher flexibility in comparison with PLGA-b-PEG-b-PLGA. This is indicated by its lower glass transition temperature. This way PCGA–b-PEG-b–PCGA chains have a more vigorous motion at body temperature and lead to a facilitated diffusion of the drug. Therefore, the release of liraglutide from PCGA–b-PEG–b-PCGA reaches almost double levels in comparison with PLGA–b-PEG–b-PLGA [47].

NPs of spherical shape have been prepared by using combined synthetic and natural polymers and were tested as insulin nanocarriers [48]. The polymers included Pluronic, chitosan, alginate, and albumin, while the physicochemical characteristics and

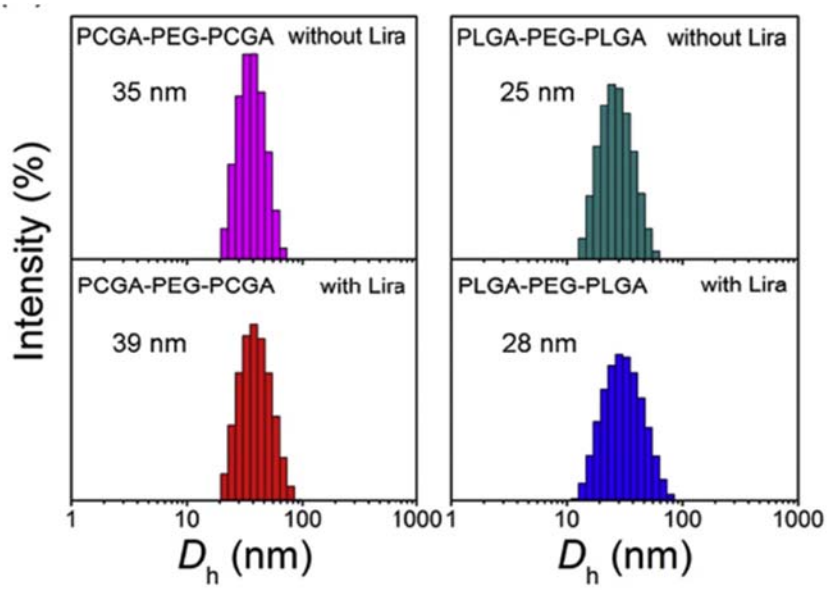

Figure 9.3
Size distributions of copolymer micelles in water, measured by DLS, without or with liraglutide, at 25 °C. *Reproduced from Y. Chen, Y. Li, W. Shen, K. Li, L. Yu, Q. Chen, J. Ding , Controlled release of liraglutide using thermogelling polymers in treatment of diabetes. Sci. Rep. 6 (1) (2016) 31593 with permission.*

hypoglycemic activity of the NPs determined their composition and polymer ratios. NPs based on poly(n-butylcyanoacrylate) had a tunable release rate of insulin depending on the monomer to insulin ratio [49]. The NPs had very good mucus penetration and stability under gastrointestinal conditions.

A summary of recent works on NPs from synthetic and biological polymers for the treatment of DM and the basic details regarding encapsulated active pharmaceutical ingredients (APIs) and administration routes for each system are shown in Table 9.1.

3. Hydrogels employed for the treatment of diabetes

A serious complication related to diabetes is the chronic wound of the lower extremities. These foot ulcers originate from the compromised presence and activity of the growth factors (GFs). Therefore, delivery of GFs directly to the ulcer site is a suggested strategy for healing. NPs loaded with the GFs named "vascular endothelial growth factor" (VEGF) and "basic fibroblast growth factor" (bFGF) were based on PLGA and Pluronic (F-127). Fibrin scaffolds were prepared by polymerization of fibrinogen (with thrombin) with the support of a poly(ether)urethane−polydimethylsiloxane layer. The GFs were loaded on the

Table 9.1: Synopsis of polymeric NPs or composite bionanosystems, their encapsulated antidiabetic APIs, and administration routes. Categorization: natural/natural* (modified)/synthetic.

Reference	API	Administration route	Polymers used as DDS	Natural/Natural*/ Synthetic
[17]	Insulin	Oral	PC6/chitosan	Synthetic/natural
[37]	Insulin	Oral	Zein-carboxymethylated amylose/chitosan	Natural*/natural
[18]	Insulin	Nasal	PEG/chitosan	Synthetic/natural
[34]	Insulin	Injectable	Acetylated dextran	Natural*
[28]	Insulin	Oral	Mucin/chitosan	Natural/natural
[20]	Insulin	Oral	Trimethyl chitosan chloride/ PLGA	Natural*/synthetic
[22]	GLP1, DPP4	Oral	PLGA (functionalized by chitosan and CPP)	Synthetic (natural)
[24]	Curcumin	Oral	Nanocurcumin encapsulated in ZnO/ chitosan NPs	Natural
[23]	GLP1, DPP4	Oral	PSi NPs/chitosan	Natural
[35]	Insulin	Tested only in vitro	Concanavalin-A/ amylopectin	Natural
[21]	Repaglinide	Transdermal	Chitosan/PLA/PCL	Natural/synthetic/ synthetic
[30]	Insulin	Oral	Chitosan/lecithin liposomes	Natural

fibrin scaffolds, either free or incorporated into the NPs. The scaffolds with the fibrin layer were applied to the skin wounds of diabetic mice, directly to the subcutaneous tissue. After 8 days of wound treatment, there was no notable change in the wound, when blank scaffolds, scaffolds with unloaded NPs, or scaffolds with loaded NPs were applied. A significant reduction of the wounds was observed only in the case of scaffolds that contained pure GFs. After 15 days of scaffold application, the wound closure was significant also for the scaffolds with loaded NPs (Fig. 9.4). It was hypothesized that the scaffolds with incorporated loaded NPs act as a release system for the GFs with a more controlled release rate that is defined by both the NPs and the fibrin network. If this hypothesis is true, the diffusion is constrained by two polymer matrices, which sustain and control the release rate of the GFs, to avoid daily drug administration. The reepithelization and tissue granulation were efficiently developed in the cases of both scaffolds (with or without NPs) [50].

Three-component hydrogels combining alginate, CHT, and poly(γ-glutamic acid) were prepared in a layered formation. The three naturally occurring polymers were separately dissolved in aqueous solutions in the proper concentrations. The layers were formed by

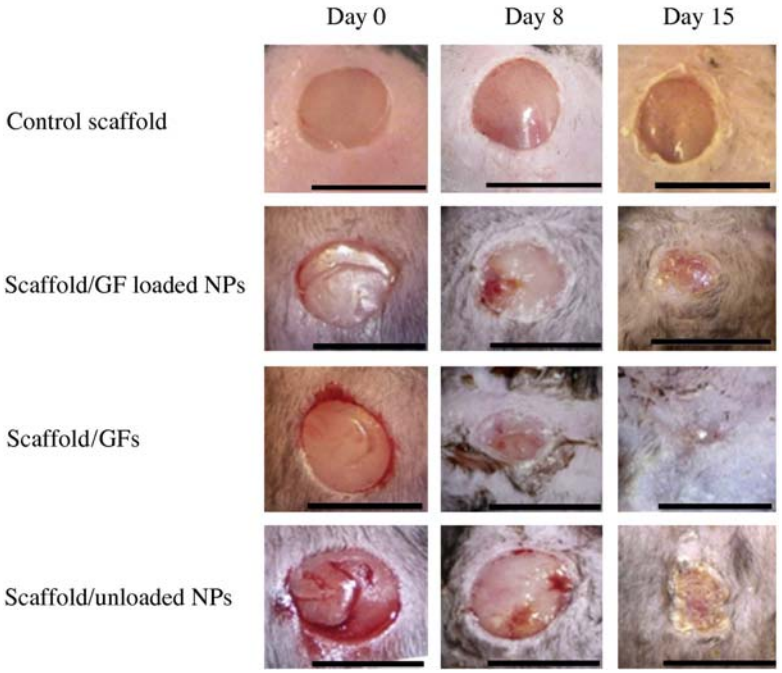

Figure 9.4

Skin wounds treated with control, GF-loaded NPs, GF-loaded, and empty NPs-loaded scaffolds, at several time intervals after wounding. The scale bar is 10 mm. *Reprinted from P. Losi, E. Briganti, C. Errico, A. Lisella, E. Sanguinetti, F. Chiellini, G. Soldani Fibrin-based scaffold incorporating VEGF- and bFGF-loaded nanoparticles stimulates wound healing in diabetic mice. Acta Biomater. 9 (8) (2013) 7814–7821, Copyright (2013), with permission from Elsevier.*

pouring separate solutions onto a glass plate and drying in sequence, i.e., alginate/CHT/poly(γ-glutamic acid). Gelation was achieved by heating the triple layer at 60°C and taking advantage of ionic interactions between alginate molecules via the introduced Ca^{2+} ions, egg–box interactions between polyguloronate groups, and ionic interactions between the carboxylate groups of poly(γ-glutamic acid) and the amino groups of CHT. The layered hydrogels showed sufficient coagulation activity that was similar for alginate-$CaCl_2$ and alginate-poly(γ-glutamic acid) layered hydrogels. This was attributed to the capability of the hydrogels to release calcium ions into the wounds, a fact that is known to support the blood clotting mechanism. Calcium ions accelerate the protothrombin-to-thrombin conversion and the synthesis and release of VII, IX, and X factors. The three-layer hydrogel was proved by histological analysis to promote remodeling and maturation of collagen in the granulated tissues. This was attributed to the presence of CHT, which can stimulate angiogenesis, formation of tissue, and optimal arrangement of collagen fibers [51].

Modified CHT in combination with synthetic polymers was also investigated [52] for diabetes-related wound healing purposes. In recent work, dual-responsive (in pH and glucose changes) injectable hydrogels from phenylboronic modified CHT, poly(vinyl alcohol) (PVA), and benzaldehyde-capped poly(ethylene glycol) (OHC-PEG-CHO) were prepared by instantaneous gelation in an aqueous solution. Morphology was checked by SEM, and the rheological properties were investigated by rheometry. The authors stated that decreasing the pH value or increasing the glucose concentration in the medium in which the hydrogel was placed resulted in an accelerated insulin release rate due to the swelling of the hydrogel matrix. Sustained pH or glucose-triggered insulin release, cell viability, and proliferation in the three-dimensional hydrogel matrix were observed, rendering the hydrogels suitable for diabetic wound repairs. The article of Zu et al. [53] is also about the formulation of a CHT/PVA composite hydrogel for the delivery of nanoinsulin. The hydrogel was formulated under the following conditions: 1.2 g of PEG, 1.5 g of CHT, 1.2 g of PVA, 1.2 mL of 1% glutaraldehyde solution, 16 mL of water, and 40 mg of nanoinsulin were mixed for about 12 min while cross-linking time was about 3 min. The nanoinsulin-loaded hydrogel was characterized using SEM, energy dispersive spectroscopy (EDS), FT-IR, DSC, thermogravimetric analysis (TGA), and XRD. The in vitro nanoinsulin release obeyed Fick's first law of diffusion, and its rate was estimated to be 4.421 $\mu g/(cm^2\ h)$.

CHT hydrogels loaded with unfractionated heparin and bemiparin were beneficial for impaired wound healing associated with diabetes, while bemiparin led to neoformed dermal tissues of better quality [54]. Hydrogels were prepared based on hyaluronic acid that was modified by the antimicrobial peptide to regulate inflammation in chronically infected wounds and with added plasma that was rich in platelets to enhance collagen deposition and angiogenesis [55]. An injectable hydrogel has been proposed to reverse the microenvironment in situations of injured diabetic hearts. The hyperbranched poly(beta-amino ester) was cross-linked by thiolated hyaluronic acid. The multifunctional hydrogel contained andrographolide NPs and nanofibers to regulate inflammatory factors, autophagy, and apoptosis [56].

Hydrogel microparticles were manufactured by radical polymerization techniques of methacrylic acid and ethylene glycol monomers. The final copolymer included poly(methacrylic acid) (PMAA), which was grafted with PEG, i.e., P (MAA-g-EG), and tetraethylene glycol dimethacrylate had been used as a cross-linking agent. The resulting powder was processed, to achieve microparticles with size in two ranges, i.e., supersmall with a size smaller than about 50 μm and larger in the order of 50−300 μm. Insulin was loaded to the microparticles by swelling them in the dry state inside solutions of the hormone. The microparticles were studied for their potential in oral insulin delivery and to optimize their size and composition. The supersmall microparticles with MAA/EG 1:1 in the molar ratio were the most effective in hypoglycemic action. The tests were performed

on diabetic rats, and the absence of absorption of insulin by the oral route without proper carriers was confirmed. The glucose levels in the blood of rats reached a minimum value after 4 h and remained low for up to 8 h. The main result of this study was that the oral administration of the supersmall microparticles in both healthy and diabetic rats could effectively control the glucose concentration in their blood, using a three-times-per-day administration and free access to water and food [57].

Hydrogels of CHT and L-glutamic acid were prepared, and they were physically cross-linked to lactic acid. L-Glutamic acid was employed because it acts as an agent for collagen synthesis. Specifically, it is a precursor of proline synthesis. SEM was used to depict and connect the rough morphology of the hydrogel surfaces with the ability for cell binding and tissue regeneration. The hydrogels had high swelling ratios in PBS, which is very important to maintain a moist environment for wound areas. They were also considered biodegradable by testing the hydrolysis of the β(1−4)-glycosidic linkage of CHT units (D-glucosamine and *N*-acetyl D-glucosamine) by lysozyme. The low solubility of L-glutamic acid in PBS was a possible cause of the observed slow and sustained release from the hydrogels. Cell viability was studied with the Alamar blue assay. The CHT/L-glutamic acid hydrogels were found of similar biocompatibility as the pure CHT hydrogels and they showed no cytotoxicity. Image analysis of DAPI-stained fibroblasts showed that the prepared hydrogels had similar cell viability to the plain CHT hydrogels. The cell attachment and proliferation were more evident in comparison with the control tissue culture. The main result of in vivo tests was that adequate adhesiveness on the wound area of diabetic rats was obtained. The hydrogels were transparent and therefore assisted transparency until complete coverage of the wound was achieved. Finally, a high macrophage influx in the inflammatory stage (day 8) was observed in the CHT/L-glutamic acid hydrogels, while epithelization was completed within 16 days due to the presence of L-glutamic acid [58].

The thermoresponsive triblock copolymer PLGA−b-PEG−b-PLGA was proposed for the development of hydrogels for the delivery of a polypeptide drug called exenatide. Two polymers of different ratios of hydrophobic to hydrophilic blocks, one soluble and one insoluble in water, had to be mixed to observe a sol−gel transition induced by temperature. The temperature of the transition and its breadth could be tailored by tuning the ratio of the two polymers. Exenatide and its complex with zinc were mixed with the polymer solutions, and its release was monitored in PBS. The mixture could form hydrogels after injection and at body temperature, stabilizing the peptide against amide bond hydrolysis. The formulation was modified by the introduction of zinc acetate so that the observed burst release was delayed by the formation of an insoluble complex with the drug. To this end, sucrose and PEG were also added, and the release was synergistically maintained for 1 week. The zinc/exenatide complex was confirmed by DLS. NPs of 250 nm in diameter were formed, whose size was unaffected by the addition of sugar and

PEG. Both the hydrogel formulations and the free exenatide were successful in glucose tolerance tests on mice. However, the hydrogels had a stronger effect on glycemic reduction [59].

The triblock copolymer PEG−b-PLGA−b-PEG forms thermoresponsive hydrogels that could successfully engraft muscle-derived stem cells in diabetic wounds to regenerate the skin tissue. The cells were applied directly to the wound surface, and the area was covered by the hydrogel. An assay of β-gal was used to count the transplanted cells remaining in the wound after a predetermined amount of time. The cells were sustained until day 9 at a percentage of 30% and at 15% until day 20. Additionally, the stem cells differentiated to fibroblasts, myoblasts, and endothelial cells at 25%, 10%, and 10%, respectively. Myofibroblasts are produced by the differentiation of fibroblasts. They exert the force that is necessary for the contraction of the tissue around the wound and toward the wound closure. This is a generally faster mechanism in comparison with epithelialization. Indeed, wound healing happened faster due to the application of the proposed system. Subcutaneous injection of the muscle-derived stem cells near the wound did not have equally good healing results. Additionally, first adding and then covering the cells by the hydrogel was the optimum protocol used, instead of adding the hydrogel with preembedded cells [59].

Hydrogels from polyacrylamide (PAA) grafted with *N*-succinyl CHT (S-CHT) were prepared as a delivery system of insulin. A ring-opening reaction with succinic anhydride was used to modify CHT, leading to substitution degrees of about (0.6−0.7). The cross-linking reaction was performed with different concentrations of acrylamide and methylenebisacrylamide cross-linker. The swelling ratio was small at low pH, because of the neutralization of the carboxyl groups in S-CHT, but it increased substantially in neutral pH. The effect was stronger for higher degrees of substitution. SEM revealed a porous morphology that could accommodate insulin, whereas the pore sizes could be reduced by increasing the amount of cross-linker (Fig. 9.5). Insulin was loaded by equilibrating the dry hydrogel in insulin solutions. PAA/S-CHT hydrogels showed a better loading capacity and encapsulation efficiency than the hydrogels with unsubstituted CHT. The amount of insulin release depended strongly on pH and the type of hydrogel. At pH 1.2, the release was much weaker than the one in the PAA/CHT hydrogels and the opposite was observed at neutral pH, where almost all insulin was released from the PAA/S-CHT hydrogel. This was related to the fact that at low pH the amino groups of CHT are protonated and repel insulin molecules (overall positively charged at pH 1.2), while at high pH the carboxyl groups of S-CHT are charged; hence they increase the swelling and the electrostatic repulsion with insulin (overall negatively charged at pH 7). Remarkably, the PAA/S-CHT system had a higher adsorption capacity for mucin and stronger mucoadhesion on the mouse intestine. Tests of the effects of the peroral administration on the liver and kidney showed no toxicity or organ damage [60].

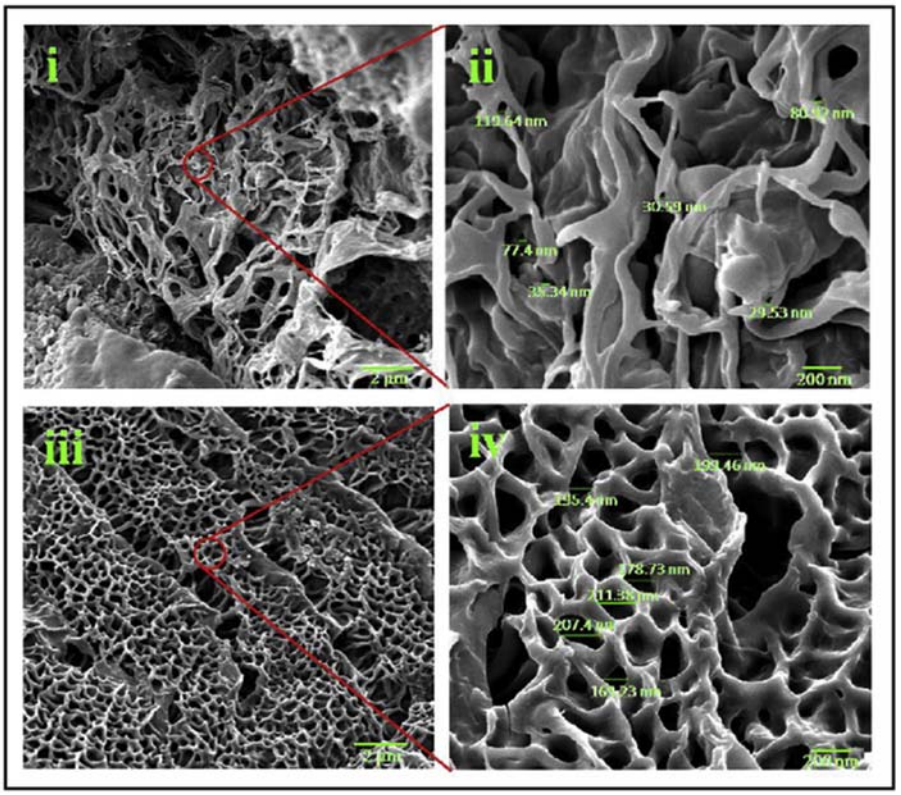

Figure 9.5

SEM images of hydrogels loaded with insulin: (i) cross-linked with MBA 0.1 g and (ii) magnified view; (iii) cross-linked with MBA 0.05 g and (iv) magnified view. *Reprinted from P. Mukhopadhyay, K. Sarkar, S. Bhattacharya, A. Bhattacharyya, R. Mishra, P.P. Kundu , pH sensitive N-succinyl chitosan grafted polyacrylamide hydrogel for oral insulin delivery. Carbohydr. Polym. 112 (2014) 627–637, Copyright (2014), with permission from Elsevier.*

Gelatin conjugated with 3-(4-hydroxyphenyl) propionic acid (HPA) was cross-linked in the presence of horseradish peroxidase (HRP), to prepare a sprayable hydrogel that can facilitate healing in diabetic wounds. The chemokines IL-8 and MIP-3a were loaded in the hydrogels, to attract mesenchymal stem cells that play a critical role in the inflammatory stage of the wound healing process. The introduction of chemokines did not compromise the mechanical properties of the hydrogel, i.e., elastic modulus and swelling characteristics. The release profiles of the two chemotactic cytokines were sustainable for longer than 7 days. However, they were different, concerning the number of positive charges and the resulting electrostatic interaction with the anionic gelatin polymer. Circular dichroism experiments on native and released chemokines showed that the incorporation in the hydrogels did not modify their secondary structure. Histological

examination of the wounds on diabetic mice was performed by hematoxylin, and eosin staining and capillary vasculature were revealed. Additionally, the CD31-positive cells (endothelial cells marked with the antibody anti-CD31) were much higher in the chemokine-containing hydrogels in comparison with the blank hydrogels. An increased percentage of epithelial layers were found in the wounds treated with the hydrogels that contained IL-8, supporting the hypothesis that chemokine attracts endothelial cells to migrate into the defective areas [61].

Dual-responsive hydrogels were fabricated based on phenylboronic-modified CHT, PEG, and PVA. The model drug was loaded in the solutions before cross-linking, which was performed in situ. Similarly, hydrogels were loaded with L929 cells. The release of insulin from the hydrogels was sustained for longer than (1−2) days. The release was enhanced under the influence of pH drop or the increase of glucose level. The benzoic imine group is pH responsive; thus, dynamic covalent cross-links are broken at low pH values. In the presence of glucose, the phenylboronic group associates with glucose and dissociates from the hydroxyl PVA group. This way, the cross-linking density drops, and the network swells, resulting in the release of insulin. The drug diffusion followed Fickian behavior at physiological pH, which is related to the hydrophilic nature of insulin. Nevertheless, the release in the presence of glucose or acidic pH followed a non-Fickian mechanism. This was suggested as a promising system because of the high levels of glucose and the low pH in the diabetic traumas [52].

A summary of recent works on hydrogels from synthetic and biological polymers for the treatment of DM and the basic details regarding APIs and administration routes for each hydrogel is shown in Table 9.2.

4. Future prospects

The current trends in polymeric bionanomaterials point to a demand for increased biocompatibility, nontoxicity, and biodegradability. Therefore, the research on materials that are based on physical interactions and involve mainly biological and biocompatible macromolecules will play a central role. Intermolecular organization of macromolecules at the nanoscale by electrostatic interactions, hydrophobic interactions, hydrogen bond, and Van Der Waals forces is promising for future developments, as they require no toxic solvents. Promising examples include the combination of anionic and cationic polysaccharides for the formation of hydrogel films [62] and the polymerization that is directed by electrostatic interactions [62]. NPs and 3D structured materials with proteins as building blocks are promising for future applications, as proteins introduce multifunctionality and specificity [63,64]. On this basis, new versatile bionanomaterials for the delivery of diabetic drugs and diabetes-related wound healing will emerge.

Table 9.2: Polymeric hydrogels are used as drug delivery systems for the treatment of DM. The table includes the APIs and administration routes for each hydrogel. Categorization: natural/natural* (modified)/synthetic.

Reference	API	Administration route	Polymers used as DDS	Natural/Natural*/Synthetic
[38]	Protein: FITC-OVA	Transdermal	Gellan gum/chondroitin sulfate/hyaluronic acid	Natural
[53]	Insulin	Transdermal	Polyvinyl alcohol/chitosan	Synthetic/natural
[52]	Insulin	Injectable	Chitosan-PBA/PVA/OHC-PEG-CHO	Natural*/synthetic/synthetic
[50]	VEGF, bFGF (growth factors)	Transdermal	PLGA/Pluronic (F-127)/fibrin/poly(ether)urethane poly(dimethylsiloxane)	Synthetic/synthetic/natural/synthetic
[57]	Insulin	Oral	PMAA-g-PEG	Synthetic
[51]	—	Transdermal	Alginate/chitosan/poly(γ-glutamic acid)	Natural
[58]	L-Glutamic acid	Transdermal	Chitosan/L-glutamic acid	Natural
[59]	Exenatide	Injectable	PLGA—b-PEG—b-PLGA	Synthetic triblock
[60]	Insulin	Oral	PAA/S-CHT	Synthetic/natural*
[61]	IL-8, MIP-3a	Sprayable	Gelatin/HPA	Natural/synthetic
[52]	Insulin, fibroblasts	Injectable	Phenylboronic CHT/PEG/PVA	Natural*/synthetic/synthetic

5. Conclusion

Simpler and less painful routes for insulin administration are still in demand for the treatment of DM. Conventional drug delivery systems that have been developed so far have several limitations, such as ineffective dosage and limited target-specificity, which may result in serious side effects. Therefore, the loading of insulin or other sugar-lowering drugs into NPs has been proposed as an alternative, noninvasive, and more suitable approach. Additionally, effective wound treatment in DM conditions has been demonstrated with the use of novel hydrogel materials, which are made of synthetic and biological macromolecules. All systems that were presented exhibit many favorable properties for these specific bioapplications. Detailed investigations on the nano- and microstructural level of these materials, as well as preclinical and clinical studies, are expected in the future, especially in the field of bionanomaterials related to DM treatment.

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SECTION 4

Constructions and other applications

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CHAPTER 10

Nanohydrogels for targeted drug delivery systems

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1. Introduction

Much recent progress has been achieved in delivering medications to our bodies. Drug delivery system development has grown exponentially. Some medications have a hurdle of low bioavailability; to counter this, hydrogels have been used as a tool to delimit low bioavailability and side effects [1]. Nanoparticle (NP) and hydrogel composite (NPH) nanoformulations play a significant role in the site-specific or targeted and regulated supply of medicinal products [2]. The field of nanotechnology comprises intracells and particles of 100 nm in size along with devices [3]. Nanoformulations can cross the blood–brain barrier, improving safety, effectiveness, and patient conformity. These formulations have the following properties: drug loading capability, drug stability, drug release rates, and targeting capacity [4–8]. Hydrogels are made of cross-connected polymers that can swell out when in contact with water or aqueous media.

Some drugs have low therapeutic efficacy, but biotechnology has made advances in developing novel therapeutic NPs. Biotechnology has made advances in developing novel therapeutic NPs [9–12]. NPs and hydrogels are two original materials that can be combined as composites to exhibit beneficial drug delivery that is absent from the individual components. NPHs can achieve a therapeutic response with a lower required drug dosage, thus reducing costs and lessening side effects [13]. NPHs are promising possible methodologies for treating glioblastoma and different cerebrum malignancy and are focused on medication delivery [14]. Researchers have studied the upsides of colon targeted delivery to improve viability by concentrating the medication particles where they are needed, thus limiting the expected symptoms, untimely arrival of medication in the upper part of the GIT, and dosing as well as extending the medication delivery period. Focusing medications within various methodologies can deliver medication to the colon

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through the oral course, including diverse detailing systems, for which medication release is constrained by various pH conditions, travel time, and intestinal microbial vegetation [15]. NPHs are also known as polymeric nanogels (NGs) or macromolecular micelles. NPHs are unique medication delivery systems with many preferences in novel medication delivery and targeted drug delivery systems. Controlled prescription release at the goal site improves activity and lessens reactions with the potential to show up at the smallest thin vessels because of their small volume and penetrate tissues through paracellular or transcellular mechanisms. Various means of administration could be organized orally, nasally, parenterally, and so on [16]. Nanocomposite hydrogels have their predominant applications in biological and material sciences [17]. The fundamental point of the proficient nanostructured delivery system is to lessen the medication portion expected to accomplish a particular remedial impact, bringing down the cost and diminishing the symptoms related to their use. In particular, this chapter features four exploration zones where NPHs have shown incredible assurance for successful drug delivery: controlled medication release, improved medication system response, site-specific medication delivery, and detoxification [18]. This chapter summarizes the structure of hydrogels, stimuli-responsive hydrogels, and intelligent hydrogels along with various aspects of their application.

2. Structure of nanoparticle–hydrogel composites

2.1 Nano- and microgel composites

The drug loading capacity of NPHs varies from inorganic NPs to biomacromolecules like enzymes and nucleic acids to hydrophobic medicines [19]. An example of an NG mix is synthetic cross-linking. Compound cross-linked NGs are more stable than physical cross-linked NGs formed by covalent connections between polymer functional groups. Noncovalent interactions (hydrogen bonds, van der Waals forces, hydrophobic bonds, electrostatic bonds) are responsible for the reversible cross-linking of NGs [20,21]. NGs are polymers, designed polymers, or polymer blends that enhance atoms, oligonucleotides, and even proteins. Luckanagul et al. [22] created thermoresponsive nanosized hydrogel particles from chitosan (a natural polymer). The polymer chitosan particles were used as spine matter coupled with poly-(N-isopropyl acrylamide) (pNIPAM). Their use for small molecule medicines, regulated drug delivery, and targeted treatment has been shown [22].

2.2 Macroscopic hydrogel composites

Different NPH systems generate various NPs injected into a bulk hydrogel system. The following techniques are used to establish a consistent appropriation [23].

2.2.1 Hydrogel development in nanoparticle suspension

The simple technique of creating a composite NPH is to gel the suspension of NPs in a hydrogel monomer arrangement. This method may be used in optically responsive optomechanical NPHs. This is due to the physical snare and the hydrogen holding links between the polymer groups and the surface of the NPs.

2.2.2 Nanoparticle preparation in situ after hydrogel gelation and later suspension of NP precursor transformation in gel

The porosity characteristic of hydrogel networks provides a nanoscopic area for NPs by avoiding agglomeration (creating an accessible space within the gel network).

2.2.3 Cross-linker specialists employed to create hydrogel matrix on nanoparticle surfaces

This method depends on the ability of NPs to connect polymer affixes or adsorb hydrogels.

2.2.4 Using nanoparticles, polymers, and a gelator to make hydrogel nanocomposites into positively charged polymers

This technique is often used for the functioning of hydrogel nanocomposites.

3. Synthesis method

Hydrogels are hydrophilic polymer networks. While most hydrogels are made from hydrophilic monomers, occasionally hydrophobic monomers are employed to tailor the characteristics for particular purposes. Hydrogels may be composed of natural or synthetic polymers. Hydrophobic monomers are synthetically derived and are more robust in comparison to naturally derived monomers. Their mechanical strength gradually deteriorates but also provides longevity. These two conflicting features should be balanced through optimal design [23]. They may also be used to produce natural polymeric hydrogels with suitable functional groups or radically polymerizable groups [24]. A *hydrogel* is a polymeric hydrophilic network connected within an elastic structure. Any technique of producing a cross-linked polymer may be used to produce a hydrogel. Hydrogels are often produced using multifunctional linker hydrophilic monomers.

The polymerizations of inverse suspension and diluted acrylamide solution, acrylic acid, and their salts were previously investigated [25]. There has been little study into the highly concentrated solution polymerization of acrylic monomers [26]. Acrylic acid-sodium

acrylate that produced a superabsorbent was developed by Chen using thermal initiator potassium persulphate [27]. Polar monomers usually include hydrogels. Their materials are natural hydrogen polymers, synthetic hydrogel polymers, and hybrids.

Preparative techniques include graft polymerization, cross-linking polymerization, water-soluble polymer network formation, and interlinking radiation. The hydrogels are light, cross-linked acrylic acid copolymers and grafted, reverse suspension polymers of emulsion and solution polymerization generated by starch-acrylic acid polymers. Polymerization techniques are discussed below.

3.1 Bulk polymerization

Many vinyl monomers may be used to produce hydrogels. Bulk hydrogels may be produced using a variety of monomers, resulting in hydrogels with specific physical features. Cross-linking agents are frequently employed in hydrogel formulations, typically beginning with radiation, UV light, or chemical catalysts. Initiator selection depends on the monomers and solvents used. Polymerized hydrogels may be produced as films, membranes, rods, particulate matter, or emulsions.

Bulk polymerization uses monomers and monomer solutions alone. A high monomer concentration produces a high rate and degree of polymerization. Conversion during polymerization, however, increases process viscosity—controlling low conversion responses eliminates these problems [28]. Bulk monomer polymerization produces a glassy, transparent, and highly stiff matrix of polymers that softens and swells in water.

3.2 Solution polymerization

Ionic or neutral monomers are mixed with the interconnector, and a UV light or redox initiator technique starts the thermal polymerization. Having a heat sink in the solvent makes polymerization of the solution preferable to bulk polymerization. The hydrogels must be washed with distilled water to remove impurities. When the amount of water exceeds the water content equal to equilibrium swelling during polymerization, a heterogeneous hydrogel develops. Mixes of water, ethanol, water-ethanol, and benzyl alcohol are popular polymerization solvents. After gel formation, swelling hydrogels may remove the synthesis solvent from water.

3.3 Dispersion method

Because the polymerization of dispersion results in powder or microspheres (beads), no grinding is necessary. The method is termed “inverse suspension” because it uses water-in-oil rather than the more common oil-in-water.

The monomers and initiator are evenly dispersed in the hydrocarbon phase based on the monomer solution's viscosity, agitation speed, rotor design, and dispersion type. Heterophase polymerizations have been widely studied [29]. The scatter is thermodynamically unstable and requires continuous agitation and a low HLB suspension agent.

3.4 Grafting to support

Typically, bulk polymerized hydrogels are fragile, but their mechanical characteristics may be improved by grafting to a more solid support. Free radicals are generated on a more robust supporting surface and are aided by monomer direct polymerization to link a chain of monomers. Hydrogels have been grafted on various polymer supports [30,31].

3.5 Polymerization by irradiation

Unsaturated compound hydrogels are produced using high-intensity ionizing radiation like gamma rays and electron beams [32–37]. Radicals form on the polymer chains while irradiating aqueous polymer solutions. In addition, hydroxyl radicals, which destroy polymer chains and create macroradicals, are produced by radiology in water molecules. Macroradicals combined on different chains create covalent bonds, leading to a cross-linked structure. Radiation initiation usually generates pure and uninitiated hydrogels.

4. Gelation mechanism

The thermally induced sol-gel transition includes hydrophobic and hydrophilic interactions. Understanding the molecular-level mechanisms of certain polymers is important for understanding gelation [38]. Hydrophobic–hydrophilic interactions are the most often observed thermal gelation. To adapt its hydrophobicity, a hydrophobic segment like methyl, ethyl, or propyl in hydrophilic polymers can be introduced [39]. The lower critical solution temperature (LCST) is the temperature at which a system becomes miscible before dividing into stages and forming gels. Polymer–polymer, polymer–water, and water–water interactions are all aqueous solutions. The equilibrium of these interactions defines the LCST system. Light dispersal rises significantly when the polymer chains collapse and consolidate during gelation [40].

Gibbs' free mixing energy regulates the quick-shift insolubility produced by thermal energy. A little temperature variation may adversely impact Gibbs' free energy [41]. As a result, water–water and polymer–polymer interactions are favored over polymer–water interactions. The entropy term should increase because of the rising enthalpy term to balance this negative change in Gibbs' free energy. Polymer chains quickly dehydrate and collapse into a more hydrophobic state at the sol-gel transition temperature. Due to hydrophobic contact, however, some copolymers of an amphiphilic block are

autoassembled in micelle structures [42]. Micelles are clusters of surfactant molecules distributed in a liquid colloid, and hydrogels may be produced by water and temperature variations. Hydrophobic micelles with hydrophilic shells are produced by these block copolymers [43].

5. Stimuli-responsive hydrogels

PEG-based polymers are often used in biomedical applications because they include cells, medications, and other biocompatible polymers in their porous matrix. If this material is supplied with a solution, its viscosity changes immediately, and the transition temperature of the sol-gel and the necessary mechanical features for on-site depot systems are achieved. Chemical agents are unnecessary in such systems, which leads to low-toxicity materials. These hydrogels are thus one of the main matrices for medicinal products and the delivery of bioactive chemical products [44]. Also of interest are the biodegradability and biocompatibility of PLGA and PCL in conjunction with PEG.

In contrast, some polymers, such as pNIPAM, create hydrogels through chemical interlinking, and to decrease formula toxicity, the chemical initiator must be removed from these systems. Hydrogel manufacturing favors physical methods, leading to the use of gels with adequate mechanical strength and the capacity to modify the drug release rate over time. One of the most recognized reasons for thermogelation is the interaction of copolymer units. In the direction of micellization, the balance between micelles and monomers is favored by the dehydration of the hydrophobic units and a new structural organization. PEG—PPG—PEG polymers may create different supramolecular lamellar-like structures by assembling themselves in micelles at the critical micellar level. The hydrophobic chains are rehydrated and the micelles reorganized under the sol-gel (Tsol-gel) solution [45–47].

PEG is frequently used as a core—shell micellar assembly in pH-sensitive drug delivery systems. The highly hydrophilic nature of PEG provides the enhanced permeability and retention (EPR) effect. The EPR effect makes it possible to keep the core—shells in circulation longer and increases the likelihood that medicine is delivered [48,49].

Immunological macrophages do not recognize PEG as additional foreign material, which allows it to remain in circulation longer than other polymers. The technique of medicine administration may reach the target organ and be absorbed by cells of a certain tissue by remaining in circulation longer [50]. This circulatory stability also permits the administration of PEG-based drugs as an injectable technique. The ionizable component is usually a peptide in pH-sensitive PEG-based copolymers. Peptides consist of amino acids, amine (-NH2), and carboxylic compound (-COOH) groups. Peptides may be cationic or anionic polymers because of the deprotonation of the amine and carboxyl groups, depending on their structure. Arginine, histidine, and lysine have cationic polymer

counterparts in copolymer architecture as positively charged amino acids. Aspartic and glutamic acids, however, are negatively charged amino acids that perform in copolymers as an anionic polymer.

Several researchers have used copolymers based on PEG as blocks, grafts, or both. Lim et al. used both graft and copolymer block techniques to develop a carrier system for transporting doxorubicin and Ce6 into cancer regions [51]. When Dox was in close proximity to the photosensitizer, a reduction in singlet oxygen formation caused an antagonistic effect. They designed a new pH-sensitive poly ionomer complex system to adjust the distance between Dox and the photosensitizer. PEG-PLL(-g-Ce6) [Chlorin e6 grafted poly(ethylene glycol)-poly(l-lysine)] was used. Furthermore, there is a grafted polyethylene glycol (PEG)-PLL (g-DMA)-PLA [2,3 dimethylmaleic anhydride grafted polyethylene glycol-poly (l-lysine)-poly (lactic acid)] polymer and tested this system against MCF-7/Dox cells for its ability to generate singlet oxygen and its antiproliferative efficacy. Compared to PEG-PLL(-g-Ce6)-PLA/Dox, the poly ionomer complex system (PIC) showed enhanced singlet oxygen production and antiproliferative effects in vitro and in vivo owing to the shift in distance between Dox and Ce6 in the PIC system under acidic circumstances.

Although the PEG block is important for initiating drug delivery, it is not the only characteristic related to drug release kinetics. Notably, pH sensitivity, not release kinetics, is a chemical characteristic of the host block. The length and chemical composition of the host block influence the kinetics of drug distribution. Mostoufi et al. studied the release kinetics of paclitaxel from a range of copolymer hybrid—methoxy-poly(ethylene glycol)-b-poly(benzyl-L-glutamic acid)—and triblock copolymers (PEG-PGA-PLeu) [52]. The authors changed the length of the nonionizable leucine chain in their study. The longer nonionizable hydrophobic area was linked to a better pH response.

6. Intelligent carrier system

6.1 pH-based intelligent system

pH-sensitive materials include cationic, anionic, and zwitterion hydrogels [53–55]. Cationic, pH-sensitive hydrogels (typically polyacrylamides) contain ionizable functional NHR, NR_2, and NH_2 groups. Amino ions are included in acidic settings. More water molecules join the hydrogel chain as ions resist one another, boosting the swelling rate. In hydrogels, alkaline–hydrogen bond interactions compress the network structure and decrease the swelling ratio [53–55].

The anionic hydrogel COO- is pH-sensitive. COO- becomes COOH in an acidic atmosphere. Group interaction compacts the structure of the hydrogel network, making water absorption more difficult. The electrostatic repulsion between carboxylic acids enhances the topology of the network and enhances water absorption and swelling [56,57].

The hydrogel of the zwitterion includes acidic groups. The real estate COOH is ionized while ammonia is protonated; −COOH is protonated and ionized in an acidic environment. When the swelling ratio approaches zero, it decreases. Ion strength influences the swelling ratio of the zwitterion hydrogel [58].

This technique is great for regulating drug release in certain areas depending on psychological needs (target). This is the most attractive technique for releasing targets [59,60]. Gastrointestinal pH ranges from 1 to 7.5 (1−3 in the belly, 5−6 in the saliva, 6.4−7.0 in the colon, and 6.6−7.5 in the intestines) (As shown in Fig. 10.1). The intelligent pH-sensitive hydrogel can sense changes in physiological environments in the body and adjust drug release.

The pH-sensitive hydrogel may effectively regulate drug release into different physiological sites via considerable pH differences between the stomach (pH 1.2) and intestinal environments (pH 7.4) [61]. The cationic hydrogel has the lowest swelling ratio and releases the least medicine under neutral conditions. Examples of drugs released from polymethacrylate copolymer hydrogels and polyacrylate dimethyl aminoethyl include caffeine. This may prevent the release of harmful drugs in a neutral oral environment and increase the aroma of the medication. The semiinterpenetrating cationic hydrogel system

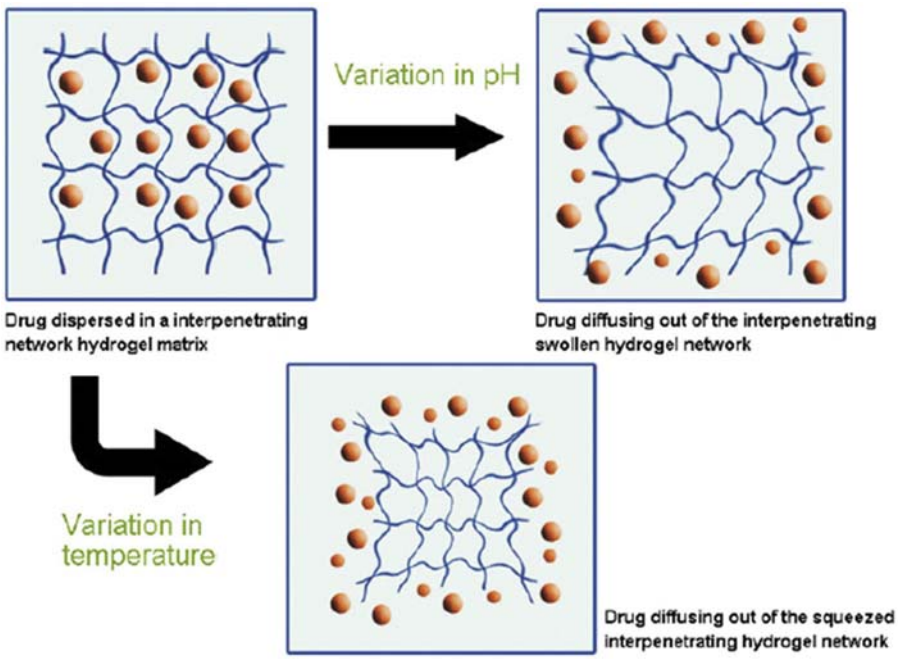
Variation in pH
Drug dispersed in a interpenetrating network hydrogel matrix
Drug diffusing out of the interpenetrating swollen hydrogel network
Variation in temperature
Drug diffusing out of the squeezed interpenetrating hydrogel network

Figure 10.1

Swelling and deswelling behaviour of interpenetrating hydrogel network with the variation in temperature and pH. *With ref from A. Vashist, H. Ahmad. Smart materials for drug delivery. Orient. J. Chem. 29 (2013). https://doi.org/10.13005/ojc/290303.*

may control the release of drugs in the stomach. For example, semiinterpenetrating chitosan and polyethylene glycol hydrogels expand quite effectively in acid (close to stomach pH). These hydrogels can deliver regulated antibiotics to the stomach. Some hydrogels have a low acid swelling ratio, and a high neutral swelling ratio may be used to provide medications for the intestines or colon [62].

6.2 Temperature-based intelligent system

Water-based gels are used in many applications, including medical devices, food packaging, and textiles. This hydrogel has hydrophobic and hydrophilic monomers. Heating or cooling a hydrogel destroys the internal structure and causes volume swelling or contraction [63]. Temperature-sensitive intelligent hydrogels are classified as LCST or upper critical solution temperature hydrogels.

The squeezing mode releases medicines by rapidly contracting the hydrogel network structure. When the ambient temperature reaches the LCST, the hydrogel contracts, releasing medicine [41]. A drawback of this process is that drugs encapsulated in hydrogel may be released too rapidly via diffusion following the LCST, defeating the purpose of long-term drug release.

The "on−off" regulating mode is further split into shell and micropore-grafted modes. The hydrogel shrinks when the ambient temperature reaches the LCST, causing the hydration shell on the surface to compress and retain water and medicine inside the hydrogel (the "off" state). When the ambient temperature is below the LCST, the compact layer on the hydrogel surface expands, allowing free drug diffusion [64]. By grafting hydrogel molecule chains into a porous matrix, the micropore grafted "on−off" regulating mode is created. When the ambient temperature is below the LCST, the grafted hydrogel chain may cover micropores in the matrix (the "off" state). When the ambient temperature exceeds the LCST, the macromolecular chain grafted onto the hydrogel shrinks, revealing micropores on the microballoon surface [65].

Due to the concentration differential between saturated medicines in hydrogels and the external environment, hydrophilic medications in swelling hydrogel may be released into the external environment when the ambient temperature is below the LCST. In case of Fickian release mechanism, the diffusion rate is linked to hydrogel swelling, drug structure, and size. The diffusion rate is linked to hydrogel swelling, drug structure, and size [66].

7. Applications

7.1 Wound healing

A "perfect" wound recovery skill must achieve rapid recovery and reduce scarfing at the base, thus ensuring capability protection [67,68]. Dermatology uses silver, gold, zinc

(metal NPs), as well as rewarding and foreshadowing bacterial infections, because of their beneficial effect on the growth of microbial growth [68]. Nonhealing wounds in type −2 diabetes are the serious consequences of a high prevalence of bacterial illness, chronic nerve and blood vessel injuries. Some causing delays in the cure of diabetes injuries include immunopathy, neuropathy, vasculopathy, and lack of developmental characteristics. Silver NPs have a strong potential to repair damage owing to their remarkable antibacterial activities. Due to the biocompatibility of hydrogel NPs, scientists have arranged silver nanoparticles (AgNPs) with impregnated chitosan-PEG hydrogels and demonstrated the ongoing arrival of AgNPs from platforms recommending improved integration of NPs into the hydrogel network. AgNPs are more practical to display antibacterial action and have a wide area that contacts a bacterium rapidly [69]. Researchers are observing the excellent antioxidant and antibacterial activities of AgNPs with impregnated chitosan-PEG hydrogels [70]. The use of several biomaterials to create hybrid complexes for advanced applications enhances antibacterial NP performance and characteristics. Zhang et al. investigated localized administration of antimicrobial therapy to develop a bioadhesive hybrid (NP−gel) NP-hydrogel. The bioadhesive NP-hydrogel hybrid (NP−gel) is created in the localized medicine delivery to improve antibacterial action. Drugs have been incorporated into NPs and integrated into a 3D hydrogel network that adheres to biological surfaces. The findings revealed that NPHs retain a regulated, extended antibiotic release profile and do not react to and are not harmful to skin. Thus, NPHs are possibly a safe and effective platform against microbial infections in localized medication delivery [71]. Researchers have studied in patients for which 75% of all fatalities are presently linked to damage or burn wound infection and over 40% of the total body surface area is burned [72]. Silver sulfadiazine (AgSD) is extensively used in the treatment of surface burn care as an antibacterial agent. The lower solubility of medicinal products and possible cytotoxicity of AgSD leads to antibacterial activity restriction. Liu et al. have investigated the use of silver sulfadiazine/nanosuspensions (AgSD/NSs) for drug administration and have increased the solubility of AgSD. Nanotechnology may be used as a novel carrier loaded with AgSD/NSs to improve AgSD antibacterial activity and minimize potential cytotoxicity. Poloxamer 407 polymer is used in the cold technique to produce thermoresponsive hydrogel filled with AgSD/NSs. This research also suggests its use as supply system for various nanocrystals and poloxamer thermoresponsive hydrogel [73]. Wound dressings have disadvantages such as insufficient antimicrobial activity, inadequate water vapor and oxygen penetration, and a lack of mechanical characteristics. Rakhshaei et al. constructed flexible hydrogel nanocomposites by mixing mesoporous silica with zinc oxide (ZnO-MCM-41) as a carboxymethyl cellulose hydrogel nanodrug carrier to overcome this inadequacy. The unique characteristics of natural polymers have been incorporated into wound dressing materials, demonstrating the cytocompatibility of nanocomposite hydrogel sheets in tissue adipose stem cells and the potential benefits of these characteristics in wound healing and dressing systems [74].

7.2 Malignancy (cancer) treatment

Uncontrolled development of irregular cells with genetic changes and epigenetic variation is termed malignancy. Radiotherapy and chemotherapy are frequently used to diagnose malignancies. The chemotherapeutic drugs cisplatin, doxorubicin, and paclitaxel have been used for many years to treat various cancers. These medicines simultaneously affect normal cells because of their lack of tumor selectiveness, producing severe symptoms, such as immunological suppression, alopecia, and inflammation of the lining of the digestive system. To address this problem, scientists have organized various hydrogel nanocomposites to concentrate on limiting the absorption of drugs into malignant cells via healthy cells and medicine supplies [75]. Losartan has been shown to efficiently reduce collagen levels in various tumors; scientists have investigated the penetration of losartan to create a hydrogel loaded with losartan NPs. The finding revealed that intratumor distribution may be increased by an NP/losartan-loaded hydrogel due to collagen depletion by losartan, and the anticancer effectiveness of NPs increased. Thus, this represents an effective approach for increasing NP tumor penetration [76]. NPHs have been shown to effectively treat brain tumors that may pass through the blood−brain barrier and destroy tumor cells without affecting healthy cells. NPHs are prospective and promising methods for treatment of brain tumors and glioblastoma, another illness [14].

7.3 Ocular drug delivery

Our eyes are our most sensitive organs. Various formulations such as eye drops are most frequently employed to treat ocular disorders. Eye drops are not bioavailable (to 5%) and have a short residence period (15−30 s), so they cannot achieve effective drug concentration in eye tissue. Frequent dosage is thus needed for effective concentration of the medication. Several nanotechnology bases have been created to improve bioadhesive development, sustained release, targeted distribution, and stimulation for eye illnesses. Some medicines are less bioavailable. The bioavailability of NPH medication may be improved via a technique to improve drug permeability and biological activity. Alruwaili et al. investigated the production of chitosan gentamycin NPs and the use of Box−Behnken statistical designs for optimization. The findings revealed that the gentamycin-chitosan sol-gel based on NPs is appropriate for ocular administration to improve corneal contact time [77]. Kabiri et al. investigated weakly accessible medicines, such as cannabis, to produce a stimulus-responsive, in situ-forming, eye-controlled NP-charged hydrogel, showing that NPHs can be used to target ocular disease [78]. NPHs show tremendous potential for administering enzyme-activated ocular medicines. Ahlen et al. formulated loaded hydrogel-driven contact lenses for the regulated administration of ocular medicines, which were produced by incorporating chitosan-poly(acrylic acid) NPs

in polyvinyl alcohol (PVA) hydrogels with in situ-gelled cellulose NPs. The hydrolysis of lysozyme chitosan chains leads to NP disintegration. The findings have shown that NP has a great potential for widespread release of the drug [79].

7.4 Nasal and vaccine delivery

Nasal drug delivery has been growing in recent years; its most promising alternatives to systematic drug delivery are restricted to intravenous administration. Research investigations have shown that several animal model analyses have shown that nanoscale carriers can enhance the administration of peptide/protein medicines and antibodies to nasals as opposed to normal treatment features. The fast mucociliary removal of the drug-loaded NPs leads to a bioavailability decrease after intranasal delivery. The research attempts to optimize residency, extend contact periods with the nasal mucosa, and improve pharmaceutical absorption to test for NPHs. Thus, the thickness of the hydrogel nanosystem (NPHs) can produce more mucoadhesive properties [80]. NPHs have numerous benefits such as improved mechanical strength and regulated delivery of the medication. Various mucoadhesive nanosystems are used to multiply the residence duration of drug formulation at the nasal mucosal location. Among the accessible nanosystems, NPH's have the characteristics of easy design, affordability, the ability to incorporate different drugs, such as hydrophilic or hydrophobic drugs, and the ability to release them at once or continuously; these characteristics show that NPHs are ideal for nasal vaccines/medications. A thermometric hydrogel formulation is an increasingly achievable and sound method for delivering medication intranasally. Some medicines, such as rivastigmine hydrogen tartrate (RHT), exhibit poor therapeutic effectiveness, and NPHs are thus used to improve medication efficacy. RHT is used for Alzheimer's disease diagnosis. Salatin et al. formatted NPHs using F-127 (PF-127) pluronic hydrogen-containing NPs incorporating eudragit RL-100 (EU-RL) in situ to improve the efficiency of RHT. Nanoformulations are produced using the cold method PF-127. RHT nanoformulation was observed with enhanced RHT permeability across the nasal mucosa. The results of our research show that nanoformulation of NPHs is extensively used for the administration of nasal medication [81].

7.5 Tissue engineering

Engineering NPHs have a key function in tissue healing (bone tissue, soft tissue, and cardiovascular tissue) [82]. Cardiovascular disease or heart failure is a clinical illness that results in permanent cardiomyocyte loss due to the imperfection of blood flow into the myocardium. Cardiovascular disease management is a major issue for healthcare providers [83]. Tissue engineering techniques have been used extensively to generate heart tissue [84]. The injectable hydrogels as an exceptional potential in cardiac tissue construction.

Researchers have investigated the use of conducting NPs of gold NPs (ANPs) to enhance the electrical characteristics of injectable hydrogels. Brisa et al. discovered that the AuNP hydrogel reverses thermal gel is promising for future cardiac tissue engineering applications [85]. Pourjavadi et al. investigated the enhancement of biocompatible polysaccharide injectable hydrogel. Injectable hydrogels avoid cell damage and death and can combine with cells or be bioactive before injection. before injection. The findings showed that the gel changed by Au-NP had increased cell adhesion and propagation [86]. The demonstrated benefits of NPs for use as hydrogel matrices may improve their performance in cartilage regeneration [87].

7.6 Vaginal delivery

The vaginal route deals with vulvovaginal problems including yeast, mold, fungal, and bacterial infections. The vaginal mucosal lining's enormous surface area and extensive blood artery network enhance drug absorption, including protein and systemic effects peptides. Recent advances have been reported in hydrogels as drug delivery vehicles for vaginal infections [88].

Vaginal inserts containing chlorhexidine digluconate [89] were made using injectable chitosan and sodium alginate. In addition to the formulation, these polymers enhance adhesion between the device and vaginal mucosa. Swelling and cross-linking, and the degree of cross-linking, are all connected to the interaction of polymer−mucin. The combination of hydrophilic carbopol 934 gel with sorbitan monostearate-sesame organogel produced a novel spreadable bigel. Its antibacterial efficacy and metronidazole release rate were higher than those of Metrogyl Gel [90].

The form of hydrogel-based doses changes depending on how they are administered; for example, vaginal dosages are usually cylindrical or torpedo-shaped. Flexible propylene glycol liposomes loaded with metronidazole or clotrimazole have been disseminated for vaginal drug administration in carbopol hydrogel. Deformable propylene glycol liposomes penetrated hydrogel more quickly than hydrogel-free liposomal preparations. Diffusion-controlled pharmaceutical release was found in in vitro studies with drug-loaded liposomes in hydrogel [91].

Antimicrobial vaginal hydrogels may act as a physical or pharmacological barrier against viral infections by restricting the passage of viruses via vaginal mucosa. Pluronic F127 and HPMC containing modified polystyrene particles in the carboxy group have reduced the motility of HIV-1 type 1, for example, by changing particle size and surface load [92]. The addition of anti-HIV CD4 M48U1 minipeptide into these polymers did not change their HIV activity, unlike conventional hydrogels. Mucoadhesion was increased by a hydrogel blend of HPMC (5% w/w) and chitosan loaded with metronidazole NPs.

The viscoelastic behavior of the novel product mirrored that of Zidoval Vaginal Gel [93]. Interesting research on chitosan hydrogel with low molecular weight revealed a significant decrease in metabolism during the development of biofilms and a reduction in total biomass to 85% [94]. The contribution of low-molecular-weight chitosan to biofilm complexity reduction may be used to treat vulvovaginitis. Pseudoplastic flow, vaginal mucosal adhesion, and enhanced antitrichomonas vaginal activity were shown to be nonirritating as a nanocapsule with indole-3-carbinol and gellan gum [95].

A novel vaginal drug delivery method using propylene glycol-liposome propylene hydrogel foam aerosol was reported. Homogeneous distribution across the vaginal epithelium enhanced adhesion properties and extended contact with the vaginal mucosa, and these effects were observed throughout the study [96]. A vaginal system was developed to overcome low solubility and bioavailability of resveratrol and epicatechin, incorporating liposomal polyphenols in the chitosan-based hydrogel. Studies of in vitro release have shown continued release, antiinflammatory effects, and excellent free radical scavenging activity [97].

7.7 Transdermal delivery

Transdermal delivery is an effective method for local or systemic effects to transport medications to the skin. Many medications, such as proteins and peptides, fail to permeate the skin at therapeutically important rates, restricting the development of transdermal therapies. Improved active chemical or physical transdermal permeability may be achieved [98]. Hydrogels supplied with transdermal drugs should be biocompatible, biodegradable, nonallergenic, easy to apply, low in water, and high in water. Hydrogels improve medicine transport through the epidermis by moisturizing the skin [99,100]. Microneedle arrays of cross-linking hydrogel polymers may absorb fluid and produce continuous channels connected to dermal circulation in the skin. Using silicone micromold templates, aqueous poly (methyl vinyl ether/maleic acid), and PEG-10,000 microneedles were produced. The release rate of the medicine was regulated by the hydrogel polymer cross-link density. Pulsatile or bolus delivery with low patient monitoring may also be electronically regulated [101]. The use of hydrogels as a microneedle patch for the continuous delivery of metformin has been investigated [102]. The hydrogel microneedle increased overall bioavailability in a rat model by almost 30% and maintained a steady-state plasma (3.2 g/mL) drug level for 24 h. Therefore, hydrogel-forming microneedle technology may be used shortly for the delivery of therapeutic drugs. The potential of iontophoresis based on a hydrogel was shown by the higher effectiveness of iontophoresis over passive methotrexate administration [103]. Carbohydrate−cationic interactions with buprenorphine induce variations in penetration rate [104]. This research utilized an electroconducting hydrogel produced from PVA embedded in polypyrene as a portable and disposable

reverse iontophoretic electrodialysis device (RED). Charge-inducing chemicals via iontophoretic units powered by RED may effectively enhance transdermal transmission of both acidic and basic medications.

8. Patents

Various researchers have patented the uses and preparation methods of nanohydrogels in recent years. Some of them are tabulated in Table 10.1.

Table 10.1: Various patents based on nanohydrogels since 2015.

Patent no.	Notes	Reference
CN108913015A	Dual network silicone hydrogel/nanosilver composite material, preparation technique, and uses disclosed. In addition to the silicone elastomer network, the compound antifouling paint contains a hydrophilic hydrogel network formed by chelating nanosilver grain and acetyl thioester link.	[105]
CN106853253A	2-Aminoethyl disulfide dihydrochloride dissolved in ultrapure water is added dropwise in W/O/W polymer emulsions and reacted to obtain PGA/Cys nanohydrogels.	[106]
CN112898601A	The invention relates to an inorganic nanoparticle reinforced chitosan-based hydrogel and its production. The invention's composite hydrogel is anticipated to be used in biomedical areas such as tissue and cell engineering.	[107]
CN106496639B	The invention is a nanocellulose—polypyrrole—polyvinyl alcohol (PVA) composite conducting hydrogel and its production technique and application are described. Makes nanocellulose; B. the surface layer of nanocellulose polymerizes to nanocellulose—polypyrrole complex. Adding a cross-linking agent and PVA to the nanocellulose—polypyrrole complex solution and stirring forms hydrogel.	[108]
CN112011067A	A degradable, self-repairing, self-adhering conductive hydrogel and method of preparation are disclosed. Examples of molecular chain entanglement and pi—pi accumulation in the hydrogel network include Schiff base and electrostatic interaction. The hydrogel degrades well under alkaline environments (pH greater than or equal to 12).	[109]
CN106750397B	The invention is a nanocellulose—polyaniline—PVA composite conducting hydrogel and its production technique and application. Synthesizes nanocellulose; B nanocellulose—polyaniline solutions are made by mixing nanocellulose and polyaniline. The hydrogel may be utilized to create flexible conducting materials with excellent application prospects.	[110]
CN109251330A	The present invention provides a nano—chitosan—PVA hydrogel, its preparation method, and its use in biomedical material technology.	[111]

Continued

Table 10.1: Various patents based on nanohydrogels since 2015.—cont'd

Patent no.	Notes	Reference
EP3494170A1	2D nanosheets exfoliated from 3D layered materials combined in a liquid non-Newtonian viscoelastic fluid to create a homogeneous composite material with enhanced tensile strength and a method for producing it.	[112]
CN108310469B	A high-performance PVA hydrogel artificial cartilage substitute material is prepared by combining a carbon nanomaterial with functional coupling agents such as polyoxyethylene ether, polysiloxane, and polyoxyethylene ether.	[113]
CN105504151A	The invention relates to the production and use of high-refraction hydrogel nanocomposites. The method's nanocomposites may be used as soft contact lens materials and implant materials for artificial corneas.	[114]
CN111825857A	The invention pertains to hydrogel technology, especially hydrogel, its preparation, and use. The hydrogel is made up of nanocellulose, polyethyleneimine, phytic acid, and soluble metal salts. The resulting hydrogel possesses high mechanical strength, conductivity, and self-healing properties. Its uses include motion sensing, tissue engineering, wound dressing, soft material drivers, flexible circuitry, etc.	[115]
CN108276593B	The invention discloses a method of producing self-repairing nanocomposite hydrogels using ultraviolet, visible, and near-infrared light induction. The invention's polymerization reaction is homogeneous; thus, the internal network structure is more uniform. Thanks to the functional nanocomposite, the hydrogel can self-heal under near-infrared, visible, and ultraviolet light, i.e., the complete spectrum.	[116]
CN106310383B	To prepare the injectable bone repair hydrogel, poly-dopamine (PDA)-modified calcium-phosphorus particles are immobilized on degradable natural macromolecules with aldehyde groups, and then the amino groups are mixed in with the degradable natural macromolecules with aldehyde groups immobilized on PDA-modified calcium-phosphorus particles. A cross-linking agent or an initiator with biological/cell toxicity is not needed to create the hydrogel. The reaction is moderate, no heat is released, no peripheral tissue damage occurs, and the technique is appropriate for clinical bone-restoration materials.	[117]
US10555831B2	Various embodiments involve putting material to a human subject's skin. The skin of a patient is treated by applying a hydrogel containing the chemical. The hydrogel and skin are chilled using a cooling applicator to treat tissue by freezing or not freezing it.	[118]
US20170325992A1	A technique and system according to one embodiment of the technology include applying a material to a human subject's skin. The applicator then cools an area of the subject. After chilling the tissue, a nucleation initiator causes a freeze event. An ice crystal may serve as a nucleation initiator by inoculating the skin and causing a predicted freeze. The time between ice crystal and skin may be adjusted to obtain desired results.	[119]

Continued

Table 10.1: Various patents based on nanohydrogels since 2015.—cont'd

Patent no.	Notes	Reference
US20170326346A1	A technique and system according to one embodiment of the technology include applying a material to a human subject's skin. The skin of a person may be changed to aid absorption. Applying a chemical to changed skin allows it to absorb it. The treatment location may be chilled to cause a skin freeze event. It may be a coupling medium that promotes or inhibits tissue freezing.	[120]
CN106076283B	The invention discloses a nanocellulose/poly-dopamine hydrogel adsorbent, its preparation method, and its uses in material technology.	[121]

9. Future directions and conclusion

The chapter explains many features of nanohydrogels, including their gelation and uses. Nanohydrogels are currently produced by several methods as described. However, performance efficiency is too low because of problems like the repeatability of the technique employed. The function of three-dimensional printing is thus essential. Three-dimensional printing provides flexible reproductivity and flexibility of molding in any form and size. NPHs are smart composite materials for their function in antimicrobial gels, light-sensitive gels, catalytic soft materials, environmental absorbents, pharmaceutical delivery, optical sensors, etc. We anticipate NPH applications to better describe the system and allow readers to develop or build novel composite smart materials for new applications. The latest entrants in the area include covalent bonds, supermolecular interactions, and novel composite hydrogels for a variety of uses.

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CHAPTER 11

Bicontinuous particle-stabilized emulsions: structural control for targeted applications

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1. Introduction

The increasing demands for new bionanomaterials having unique structures and adaptability for a wide range of applications in energy, environmental remediation, biomedicine, foods, agriculture, and pharmaceutical products are being faced with growing limitations in material fabrication [1,2]. Using biological units such as carbohydrates, enzymes, proteins, and hormones, new biobased polymeric gels [3], emulsions, and foams [4] can be manufactured using new techniques in nanofabrication. To meet these challenges in the field of biotechnology, miniaturized emulsion systems such as micro- and nanoemulsions have been developed to provide advanced applications in drug delivery, biological or diagnostic agents, and other uses requiring increased bioavailability. Of interest to the bionanotechnology field are biphasic nanoemulsions in the forms of oil-in-water (O/W) dispersions, water-in-oil (W/O) dispersions, or bicontinuous nanoemulsions.

Broadly, nanoemulsions offer unique morphological advantages for the encapsulation and release of bioactive materials with high bioavailability. Nanoemulsions serve as substitutes for liposomes and vesicles owing to their extremely small droplet sizes, improved bioavailability, nontoxicity, nonirritancy, and long shelf life. Moreover, they provide high surface area emulsions for greater absorption, high uptake of oil-soluble supplements in cell cultures, and strong solubility for lipophilic drugs. Formulating nanoemulsions involve the use of the following materials: (1) an apolar phase including oils such as castor oil and olive oil, (2) aqueous solvents that are mostly designed to form a continuous phase surrounding the dispersed oil phase, (3) emulsifying agents such as surfactants forming monomolecular or multimolecular films at the oil−water interphase, and in certain cases (4) solid particles with near equal wettability for both polar and apolar phases, populating the interface to provide a barrier against coalescence [5].

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In a typical example of formulating nanoemulsions to increase the loading capacity of lipophilic active ingredients, high energy input via high-pressure homogenization, rapid stirring, or ultrasonication can be combined with high surfactant loadings to create extremely small sizes of thermodynamically stable droplets. Alternatively, low-energy emulsification routes such as temperature-controlled phase inversion and emulsion inversion can be used. The creation of a miniaturized droplet system with tunable charge and rheology in nanoemulsions provides rapid digestibility, increased drug loading, high bioavailability, and high surface area for enhanced exchange of bioactive materials. This unique feature in nanoemulsions presents diverse opportunities in the food and drug industry including uses in topical, ocular, intravenous, and oral delivery [6,7]. Although nanoemulsions offer enhanced bioavailability, their extremely small sizes make them susceptible to Ostwald ripening, leading to creaming or flocculation and generally short shelf lives. The use of ripening inhibitors or surfactants can help to impart long-term stabilities for nanoemulsions, creating a sustainable clear liquid formulation for broad applications in controlled drug delivery and transdermal applications. To further improve their stability, surfactants are carefully selected to obtain an ultralow interfacial tension in nanoemulsions. Lastly, the use of high surfactant concentrations in a mobile fluid medium helps to stabilize the high interfacial area developed during homogenization processes in nanoemulsion formulations.

Another key component of the bionanotechnology industry is developing new materials from naturally derived sources to reduce the cost of production and protect the environment. To reach this goal, organic-based liquids and colloidal particles can be readily self-assembled into nanostructured emulsions and gels tailored for emerging bionanomaterial applications [8,9]. Emerging liquid-based materials known as bicontinuous interfacially jammed emulsion gels (bijels) present unique opportunities in the bionanotechnology industry [10]. Bijels are suitable for developing new bionanomaterials where fundamental surface science, colloidal chemistry, and interfacial phenomena are relevant. In this chapter, bijels are introduced as a new class of nanocomposite and amorphous soft-solid material for bionanotechnology purposes. Bijels are made of a bicontinuous arrangement of thermodynamically incompatible liquid phases with nanoparticle-enriched interfaces giving rise to a high surface area membrane material for high interfacial exchange, immobilization, and separations [11−13]. The invention of bijels can be traced to the idea of scientists at the University of Edinburgh, asking if spontaneous self-assembly in nonequilibrium processes can be used to develop particle-stabilized emulsions with bicontinuous architectures [10,14].

Generally, particle-stabilized emulsions, also known as "*Pickering emulsions,*" were introduced in the 20th century by pioneers working in emulsions research; notable among them were Professor W. Ramsden (1868−1947) and Umfreville Pickering (1858−1920) [15]. Unlike common emulsions where molecular surfactants are used as interfacial

stabilizers, the use of solid particles as stabilizers impart Pickering emulsions with more robust features [16]. Pickering emulsions also present the ability to derive convoluted shapes and sizes for applications benefiting from notably high surface areas, high porosity, and percolating channels in emulsion template designs [4,17]. Moreover, the use of a wide range of colloidal particles, including carbon-based nanoparticles, ceramic nanoparticles, metal/metal oxide nanoparticles, semiconductor nanoparticles, polymeric nanoparticles, and lipid-based nanoparticles for the synthesis of Pickering emulsions further broadens their scope of applications [4]. Additionally, unique benefits can be derived from the particulate components in Pickering emulsions based on the functionality of the interfacial sequestered particles. For example, particles at emulsion interfaces can serve as catalyst sites for the high-yield reaction process [18,19], porous scaffolds for regenerative biomaterials, and other tissue engineering applications [20]. Similarly, high surface area membranes can be derived from particle-stabilized emulsions for filtration, purification, catalysis, and antifouling purposes [21,22]. To stabilize Pickering emulsions, colloidal particles with a radius (r) and a three-phase contact angle (θ) are sequestered at the interface of two immiscible phases, usually made of oil (O) and water (W). The oil−water (O−W) interface has an interfacial tension (γ), allowing for those particles to be trapped with attachment energy (E), usually defined by the equation, $E = -\pi r^2 \gamma(1 - \cos\theta)^2$. Fig. 11.1A shows examples of emulsions or gels having different structures based on the interfacial properties of colloidal particles used to stabilize O−W interfaces.

Irrespective of the processing history of particle-stabilized emulsions, the particle contact angle, θ, determines the morphology of the Pickering emulsions formed [23]. Generally, oil-in-water (O/W) emulsions form when more hydrophilic particles ($\theta < 90°$) are used as shown in Fig. 11.1A-i, whereas water-in-oil (W/O) emulsions are formed using more hydrophobic particles ($\theta > 90°$) as shown in Fig. 11.1A-ii. In a special case where the particles have approximately equal affinity for both oil and water phases (i.e., $\theta \approx 90°$), a nonpreferential curvature emerges.

Understanding the conditions required to form bicontinuous arrangements of liquids using colloidal particles, Stratford et al. (2005) used lattice Boltzmann computer simulations to show how bijels can be derived via the self-assembly of bicontinuous structures with interfacially trapped particles [14]. Their work showed how three-dimensional (3D) bijels can be generated using near-neutral ($\theta \approx 90°$) colloidal particles to arrest the spinodal phase separation of biphasic liquids.

In bijels, both immiscible liquid phases are interconnected with a percolating layer of particles separating either liquid. Hence, unlike droplet-based emulsions with limited surface area and transport properties, biomolecular components contained in bicontinuous fluids can be conveyed in opposite directions through bijel channels with the ability to efficiently exchange various molecular species at their interfaces as shown in Fig. 11.1B.

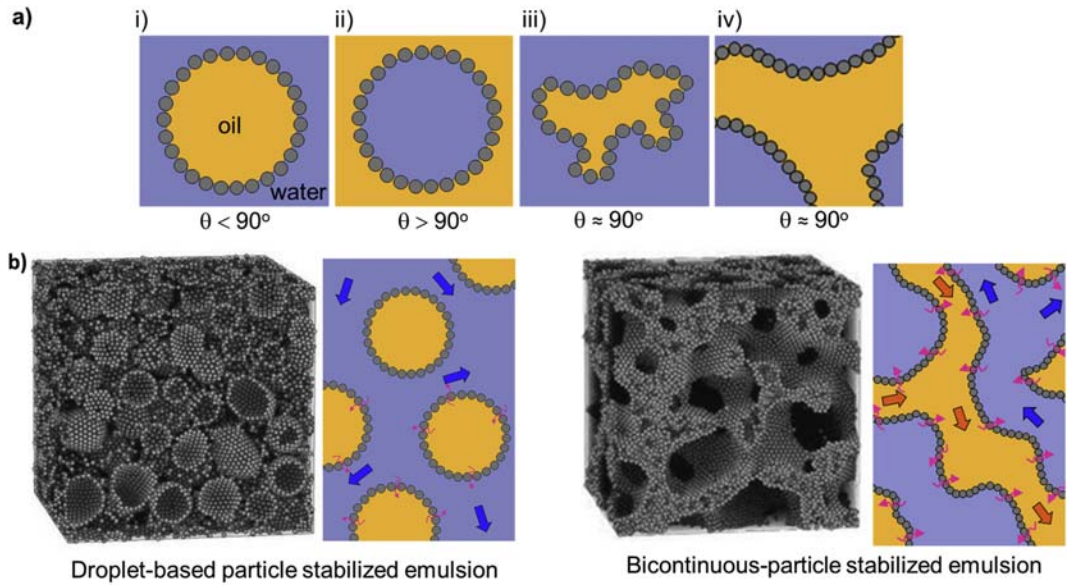

Figure 11.1

(A) Different types of particle-stabilized emulsions based on the contact angle of particles used as interfacial stabilizers. The water phase is colored blue, whereas the oil phase is colored yellow with grey-colored particles having different wettabilities, ranging hydrophilic (i), hydrophobic (ii), and near-neutral (iii and iv), sequestered at the oil—water interfaces. (B) Features of particle-stabilized emulsions differentiating droplet-based emulsions with limited surface area and transport properties (left) from bicontinuous particle-stabilized emulsions with high surface area and advanced biphasic transport properties (right). *From Copyright 2011, F. Jansen, J. Harting, From bijels to pickering emulsions: a lattice boltzmann study, Phys. Rev. E - Stat., Nonlinear Soft Matter Phys. 83 (4) (2011). https://doi.org/10.1103/PhysRevE.83.046707.*

Following the computational work in 2005 [14], bijel materials were synthesized for the first time in 2007 by Herzig et al. (2007) [11]. Their experimental work demonstrated that two biphasic liquids can be tortuously entwined to form a high surface area emulsion gel material having cocontinuous interfaces separated by a stabilized layer of colloidal particles. Inherent in bijels are unique features such as hierarchical or uniform porous materials with large surface areas, tunable morphologies, efficient transport features, and improved structural integrity. Based on their distinctive properties, bijels present exciting opportunities proposed for the generation of new biobased composite materials ranging from liquid-based emulsions or gels for drug delivery [24,25], and solid-based materials including polymer bionanomaterials for tissue engineering applications [20,26].

Moreover, unique physical, chemical, and biological properties can be derived from bijel-based bionanomaterials where their structural features can provide a further understanding of self-assembled processes, colloidal systems, and interfacial phenomena

concepts relevant for the biotechnology industry. Already, bijel-based systems have been demonstrated for use as membranes for wastewater purification [21], biphasic channels for significantly improved reactions and separation [19,24], cell delivery and cell growth scaffolds for medical implants [20,26], high-performance catalytic systems [24], encapsulation and release materials [25,27], high surface area sensors [28], controlled drug delivery [27], energy storage materials including batteries [29], supercapacitors and electrodes for fuel cells [30,31], and food applications [32].

This chapter explores the potentials of integrating bijel materials in a wide range of bionanomaterial and bionanotechnology applications. Sections 2 and 3 describe the various methods used to fabricate bijels, and how their structures are tailored to those applications. In Section 4, the potential uses of biological entities in the fabrication of bijels are discussed, describing how, for example, organic-based materials, naturally derived colloidal particles, and natural functional chemistries can be used. Section 5 describes how bijels are engineered for various applications ranging from drug delivery, foods, tissue engineering, and filtration membranes. General conclusions and future perspectives on bijels relevant for the bionanomaterial and biotechnology industry are discussed in Section 6 of this chapter.

2. Methods of bijel fabrication

Bijels have recently piqued the interest of different scientists working in fields where gels, emulsions, and colloids are used to make micro- and nanomaterials due to their high surface areas and combined structural, mechanical, and multifunctional properties [33]. Unlike typical emulsions having one liquid phase dispersed in a continuous phase [23], bijels have both liquid phases arranged in a cocontinuous and bicontinuous network [11]. In view of the wide range of potential applications to be developed from bijels, scientists have explored different methods such as (1) thermal quenching of biphasic liquids [11,13], (2) solvent transfer induced phase separation (STrIPS) [12,25], and (3) direct mixing, to fabricate bijels [34,35]. In this section, different methods of making bijels are discussed, with focus on their processing parameters with potentials to be adapted for bionanomaterial applications.

2.1 Thermal quenching of biphasic liquids via spinodal decomposition

Typically, thermodynamically incompatible liquids (e.g., oil and water) do not mix to form a monophasic fluid, but they can be intimately brought together via vigorous mixing, temperature changes, or by the addition of a cosolvent. Subsequently, when the mixing component is removed, both liquid phases undergo a process of relaxation and phase separation, with the constituent liquids proceeding toward the configuration of the

minimum interfacial area to release the energy generated by interfacial tension [36,37]. By heating oil and water at different compositions, both liquids can be homogeneously mixed in the monophasic region above the binodal line and the upper critical solution temperature (UCST) as shown in Fig. 11.2A. Upon cooling the same monophasic mixture, an oil–water phase separation front evolves, and the mixture undergoes demixing, either taking the path of nucleation and growth, or spinodal decomposition. The path taken is usually determined by the composition of the oil and water mixture, as well as conditions such as the cooling rate influencing the process of thermal quenching.

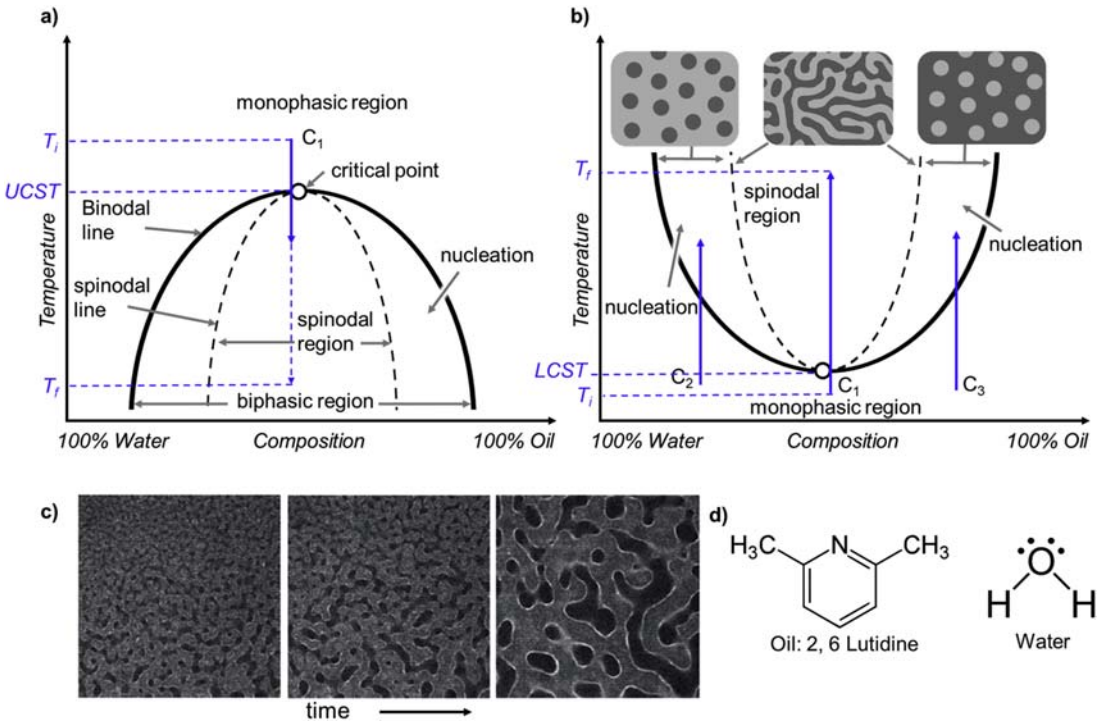

Figure 11.2

Methods of making bijels by thermal quenching. (A and B) Temperature changes are used to access the spinodal region of liquid–liquid phase separation to derive bicontinuous domains for bijel fabrication for both upper critical solution temperature (UCST) systems (A) and lower critical solution temperature (LCST) systems (B). The gray areas indicate the water phase, whereas the dark area represents the oil phase. (C) Confocal microscopy images showing a typical process of spinodal decomposition leading to the stabilization of bijels made with water and oil phases. Percolating the bicontinuous network is colloidal particles trapped at the oil–water interface. (D) Chemical structures of a sample liquid-pair (lutidine and water) used for bijel fabrication. *From Nature Publishing Group, Copyright 2007, E.M. Herzig, K.A. White, A.B. Schofield, W.C. Poon, P.S. Clegg, Bicontinuous emulsions are stabilized solely by colloidal particles, Nat. Mater. 6 (12) (c. 2007) 966–971 [38]. https://doi.org/10.1038/nmat2055.*

To make bijels using the UCST method, a critical composition (C_1) of monophasic oil and water mixtures at an initial temperature (T_i) is cooled to a final temperature (T_f). This results in liquid−liquid phase separation to produce bicontinuous oil and water channels within the spinodal region. Alternatively, when the water fraction is high (C_2), the spinodal region is not accessed as shown in Fig. 11.2B. Instead, the kinetic path of thermal quenching enters the region between the binodal and spinodal line, causing the nucleation and growth of oil droplets dispersed in a continuous phase of water, hence forming an O/W emulsion. On the other hand, when the oil fraction is relatively high in the starting composition (C_3), water droplets are formed in a continuous oil phase, described as a W/O emulsion. Hence, the selection of a critical composition (typically, 50:50 oil and water compositions) is important for the demixing route to access the spinodal region where bicontinuous channels may form. In a similar method of accessing the bicontinuous regime, a lower critical solution temperature (LCST) approach is used as shown in Fig. 11.2B. In the LCST method, a monophasic oil and water mixture, usually starting at room temperature (RT), is heated to induce spinodal phase separation starting with a critical composition (C_1).

Using the LCST method, Herzig et al. (2007), demonstrated the first-time fabrication of bijels using a critical monophasic composition of 2,6-lutidine (hydrophobic phase) and water (hydrophilic phase), at a starting temperature of 33.5°C [11]. Upon heating the mixture to about 40°C, the oil and water components undergo demixing and spinodal phase separation. As new bicontinuous interfaces evolve, neutral wetting (i.e., $\theta \approx 90^\circ$) colloidal silica particles are swept to and irreversibly trapped onto the spinodal interfaces. As time proceeds, the sequestered particles are pushed close to each other on the bicontinuous interfaces wrapping around the coarsening liquid−liquid domains. Eventually, the overall surface area of the bicontinuous liquid−liquid interfaces available for the particles to attach slowly decreases, eventually locking the interfacially jammed particles in place with significantly high attachment energy (>1000 kT) [39] to stabilize a 3D bicontinuous network. The jammed particles stop the phase separation process resulting in permanent stabilization of bijel materials. In this method, the colloidal particles need to be carefully treated to have a contact angle not differing greatly from 90°. Otherwise, a preferential curvature is induced at the interface, forming droplet-based particle-stabilized emulsions (i.e., Pickering emulsions) instead of bijels, even though the route of spinodal decomposition was taken. The challenge faced with this approach was that the careful tuning of the colloidal particle surface chemistry was tedious. Additionally, there is a limited range of immiscible pairs of liquids to be selected for making bijels via the LCST method [16,26].

Inspired by the several available opportunities to develop bijels for different applications, multiple research groups have used the LCST approach for multiple applications [11,13,40]. In one scenario, fluorescent silica microspheres with radii of 375 nm were

suspended in a critical composition mixture of the water and 2,6-lutidine. The immiscible liquids underwent spinodal phase separation upon electromagnetic irradiation [13]. Uniformly porous bijels with a thickness of several millimeters were created showing an interpenetrating network of bicontinuous domains with approximately a monolayer of particles sequestered at the liquid–liquid interface. To maintain their bicontinuous structures, bijels fabricated via the LCST approach need to be maintained above room temperatures (preferably, 40–60°C), where the selected liquids (e.g., water and two to six lutidine) remain phase separated. This makes the bijel material incompatible with normal applications that require processing at room temperature. To maintain a rigid bicontinuous state in the LCST system for long-term use, one of the liquid phases of the bijel network can be polymerized to create a solid porous scaffold [13].

To create more stable bijels without solidifying either liquid phase, the UCST method is suitable, especially since the casting formulation is thermally quenched from a higher temperature (T_i) to a lower temperature (T_f), usually below room temperature. Using a mixture of ethanediol and nitromethane, research scientists have demonstrated the formation of bijels via the UCST method, forming bicontinuous networks with long-term stabilities at room temperature [27].

Besides using temperature to control the mixing or demixing of incompatible liquids, cosolvents such as alcohols can be used to mix the immiscible biphasic components and create monophasic fluids for bijel fabrication. Like the thermal quenching method, the route of spinodal phase separation can be accessed by manipulating the solvent composition in ternary mixtures made up of a hydrophobic phase (e.g., oil), a hydrophilic phase (e.g., water), and a solvent component (e.g., alcohols) [12,36]. Moreover, careful control of both the ternary-phase equilibria and the particle surface chemistry facilitates the stabilization of bicontinuous structures [25,41]. This approach, known as solvent transfer–induced phase separation (STrIPS), provides a versatile and highly scalable approach to produce different bijel materials, including microparticles and bulk fibers [12,25], hollow fiber membranes [21], bijel bundles, and high tensile ropes [42] in a continuous manner.

2.2 Solvent transfer–induced phase separation

As discussed earlier, the basic components of making bijels involve the use of binary liquids having dissimilar thermodynamic compatibility. Like a mixture of oil and water, the addition of a cosolvent can enable the mixing of the original immiscible liquids to create a ternary mixture. The major benefit of STrIPS is that a wide range of nonpolar liquids can be selected and mixed with polar liquids using different organic solvents to prepare the starting ternary mixture. Hence, bijel material properties unique to the selected liquid phases can be derived and tailored for bionanomaterial applications such as foods,

pharmaceutical products, filtration membranes, enzymatic reaction media, and drug delivery. Another advantage is that, unlike the LCST thermal quenching approach, all immiscible liquid pairs selected for bijel fabrication via STrIPS are applicable to room temperature conditions, further expanding their utility in industry.

The STrIPS method is like the process known as the "Ouzo effect," where a monophasic ternary mixture system comprising ethanol, water, and anethole is introduced into water [43]. The dilution of the cosolvent (alcohol) causes the uniform ternary mixture to cross its binodal line in the ternary diagram to induce phase separation of the incompatible liquids—water and anethole. Therefore, the starting composition of the ternary mixture (i.e., volume fractions of respective liquids) determines the path of phase separation, whether spinodal decomposition or nucleation and growth [36].

When a ternary mixture composition made up of 47% solvent (alcohol), 28% oil, and 25% water is selected (demonstrated as C_1 in Fig. 11.3A), the path of spinodal decomposition can be accessed by reducing the solvent component. Typically, in STrIPS, the organic solvent phase is removed by introducing the ternary mixture into an external continuous stream of water as shown in Fig. 11.3B. As spinodal decomposition proceeds, cocontinuous channels of the oil and water phases are created with a thin bicontinuous interface separating the immiscible liquids (oil and water). To develop bijel systems suitable for bionanotechnology applications such as drug deliveries and food technologies, different biological macromolecules can be introduced into the ternary mixture. The biological entities will partition into either a liquid phase (oil or water) based on their hydrophobicity index. The presence of interfacial stabilizers such as surface-active spherical colloidal particles in the ternary mixture causes the bicontinuous interfaces to be stabilized by these particles to arrest the process of oil−water phase separation to form bijels. In most STrIPS bijel fabrication protocols, surfactants have been used to render the colloids phase neutral to facilitate the interfacial stabilization of bicontinuous structures [12,19,25,42].

Essentially, silica nanoparticles at different pH values are easily dispersed in polar liquids such as water. By adding nonpolar liquids such as oils and alcohols, the dispersibility of silica in the complex fluid mixture environment (water, oil, and alcohol) is significantly reduced. This occurs because, the silica surface is covered with hydroxyl (OH) groups, making the particles hydrophilic, and thus incompatible with the more hydrophobic liquids. When surfactants (e.g., alkyl trimethylammonium cations) interact with silica particles, their hydrophobicity increases, making those modified particles more compatible with the nonpolar (hydrophobic) liquid phase [41]. This important approach facilitates the dispersion of colloidal particles in the ternary mixture needed to prepare the starting formulation for bijel formation via STrIPS.

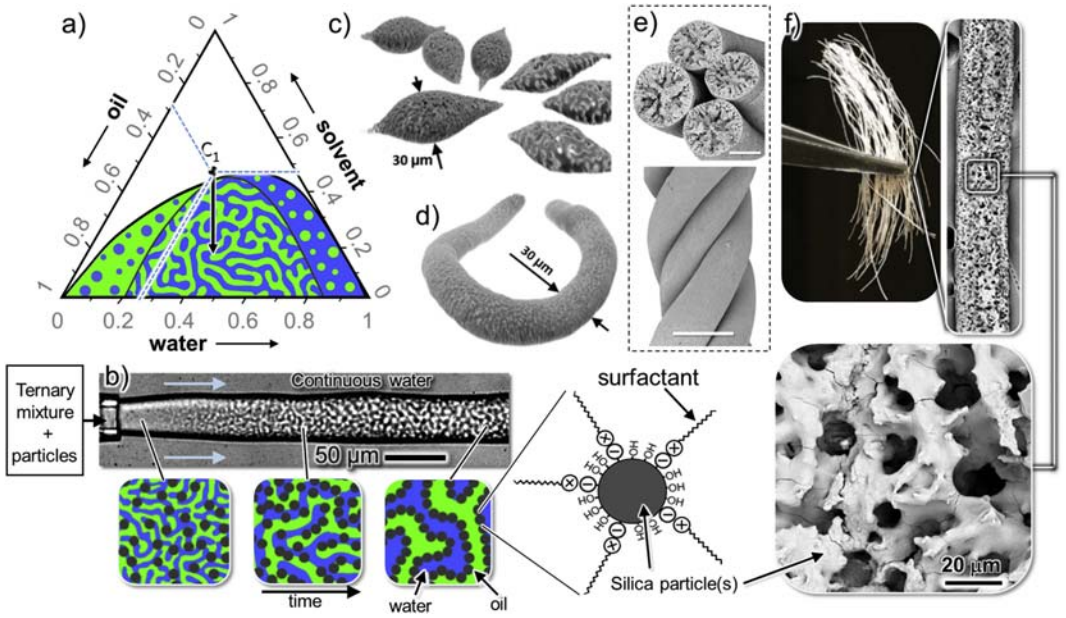

Figure 11.3

Making bijels via solvent transfer–induced phase separation (STrIPS). (A) Ternary phase diagram made up of a hydrophilic liquid (water), a hydrophobic liquid (oil), and a cosolvent used to prepare the starting formulation for STrIPS bijel fabrication. (B) Microfluidic extrusion of a ternary mixture into an external water bath to cause liquid–liquid phase separation. (C) Bijel capsules formed using the STrIPS method by controlling droplet-pinch off behavior . (D) Bijel fibers formed by STrIPS. (E) Bijel bundles formed by microfluidic twisting of fibers produced via STrIPS to generate high-tensile-strength ropes. (F) Bijel fibers showing the porous bicontinuous network with colloidal particles anchored at the interface. *(B–D) From Copyright 2015, M.F. Haase, K. J. Stebe, D. Lee, Microparticles: continuous fabrication of hierarchical and asymmetric bijel microparticles, fibers, and membranes by solvent transfer-induced phase separation (STRIPS), Adv. Mater. 27 (44) (2015) 7065–7071. 10.1002/adma.201570297; (E) Copyright 2015, S.P. Kharal, R.P. Hesketh, M.F. Haase, High-tensile strength, composite bijels through microfluidic twisting, Adv. Funct. Mater. (c. 2020). https://doi.org/10.1002/adfm.202003555; (F) Copyright 2019, S. Boakye-Ansah, M.S. Schwenger, M.F. Haase, Designing bijels formed by solvent transfer induced phase separation with functional nanoparticles, Soft Matter, 15 (16) (2019) 3379–3388. 10.1039/c9sm00289h.*

Most essentially in the STrIPS method of making bijels, nanoscopic and microscopic bijel features can be controlled based on the in situ modification of colloidal particles with surfactants. In addition to the surfactants facilitating particle dispersion in ternary mixtures, factors such as (1) concentration of surfactants [12,25], (2) tunable hydrocarbon chain length of the surfactants [25], and (3) surface charge density of the particles [41] can be used as a control knob to manipulate the morphology of STrIPS bijels. Also, based on the type of particles to be used in the ternary mixture, different surfactants at varying concentrations can be selected, chiefly to enhance particle dispersion in the ternary

mixture and to control bijel structure. For example, with the use of more hydrophilic particles, surfactants with strong hydrophobic moieties are needed to make the particles surface active and to form bijels [25].

Given the growing need to develop novel applications in bionanomaterials and bionanotechnology, new bijel materials made without the use of surfactants are needed. Most molecular surfactants are biologically incompatible for applications requiring contact with living tissues or exposure to the environment. Hence, new routes to fabricate STrIPS bijels without using surfactants were envisioned by scientists working in this field of research [25,44]. This is an important approach to expand the utilization of STrIPS bijels for a wide range of applications to prevent allergic and carcinogenic effects. For example, researchers have recently demonstrated the fabrication of STrIPS bijels using both hydrophilic and hydrophobic particles in the ternary mixture suspension without using surfactants [45]. By controlling the volume fractions of the hydrophilic and hydrophobic nanoparticles, stable bijels were formed based on the polarity of the oil component.

Moreover, the surface modification of particles via direct covalent attachment with hydrophobic functional groups can also be used to generate surface-active particles for STrIPS bijel formation [25]. Instead of using an in situ modification of surfactants, the wetting properties of nanoparticles can be manipulated by attaching, for example, organosilane groups. This method involves chemically grafting molecules or polymers on the surface of particles using covalent bonding to tune particle wettability or induce stimuli-responsive features. Hence a wide range of biomolecules such as proteins and DNA can be conjugated with colloidal particles, presenting an innovative and powerful approach to develop novel biofunctionalized particles for bionanotechnology applications [44,46]. For example, biomolecular groups such as carbohydrates, peptides, nucleic acids, and antibodies can be attached to gold and iron oxide nanoparticles to impart biosensors, bioanalysis, biolabeling, and bioimaging features [47]. Moreover, biogenic synthesis of nanoparticles presents an interesting approach to use natural products comprising plants, algae, fungi, and yeast as naturally occurring biomolecules to synthesize nanoparticles having different shapes and sizes [48]. Using naturally synthesized nanoparticles, novel bijel materials can be designed in a greener, safer, and more environmentally friendly approach.

Such naturally derived conjugation chemistries can combine the characteristics of both materials, such as the spectroscopic features of the nanoparticles, and the biomolecular capabilities of the attached biofunctional groups to provide synergistic functions. Using the method of STrIPS, which can uniquely embrace a variety of oil−water pairs and different colloidal particles, biologically modified particles integrated into this process will open new doors in the food/nutrition, agriculture, cosmetics, pharmaceutical, and other bionanotechnology-driven industries.

Already, the STrIPS method has shown promise to utilize different functional nanoparticles to be dispersed in ternary mixtures via careful modification of the particle surface chemistries [25,41]. This would enable STrIPS bijels to be fabricated, not only with silica particles but also with other particles, such as alumina, magnesium oxide, gold, carbon nanotubes, and layered double hydroxides. Additionally, since a wide range of oils can be used in the STrIPS method, it promotes the development of bijel technology in several industrial applications. For example, using bijels as micro- and nanostructured emulsion systems, essential oils ranging from terpenes, carotenoids, and flavonoids can be encapsulated and released in a controlled fashion. This would extend the utility of bijels as antibacterial food preservatives and as a treatment for antiinflammatory, bactericidal, fungicidal, antioxidant, and virucidal applications [49–51].

Therefore, it is significant for scientists and engineers working in this emerging field of research to find the desired combinations of hydrophobic and hydrophilic liquids to be mixed with a cosolvent and biobased particles and used as basic materials for bijel fabrication. So far, the STrIPS approach has been diversified to fabricate different bijel materials, including microparticles, bulk fibers, planar films, hollow fiber membranes, twisted fiber ropes, and planar membranes as shown in Fig. 11.3C–E. A combination of these unique strengths in the STrIPS approach would enable the scalable and continuous fabrication of bijels using tunable bionanoparticles serving as catalytic reactors [24] and drug delivery hosts [25,27]. Moreover, with bijels presenting high interfacial area between the biphasic liquid interfaces, efficient exchange of chemical substances can be realized to provide high product yields in applications such as continuously operated biphasic chemical reactions [10,19]. More details about these applications are later discussed in Section 5.

In an alternative approach to making bijels, researchers have attempted to preclude the use of the more common route of spinodal decomposition to make the fabrication process much simpler. In the next section, one of those routes using direct mixing of the liquid–liquid components with colloidal surfactants as interfacial stabilizers is discussed.

2.3 Direct mixing method

Besides using spinodal decomposition as the major route to form bijels, simpler methods of generating gyroid interfaces are needed to extend their applications. Such routes are needed, especially in cases where the used liquid pairs are strongly dissimilar and very difficult to be mixed. Making bijels via spinodal decomposition requires colloidal particles with well-defined wetting properties ($\theta \approx 90^\circ$), which sometimes pose a significant challenge [11,52]. Alternatively, shear mixing strategies can be used to create a high interfacial area between immiscible liquids and stabilized at their interfaces with colloidal particles [52]. The creation of bicontinuous interfaces via shear mixing can be used to

form bijels by inducing interfacial assembly of a jammed nanoparticle film to indefinitely arrest Plateau−Rayleigh instabilities [34]. Without the sequestered particles, the nonequilibrium liquid phases recoil to form droplets to minimize their surface area [53].

Two different groups have demonstrated the direct mixing approach of forming bijels independently [34,35]. Huang et al. (2017) mixed nearly equal volumes of an aqueous phase and a nonaqueous phase by vigorously stirring the immiscible liquids and trapping the generated bicontinuous interfaces with nanoparticle surfactants made of COOH-functionalized nanoparticles (located in the aqueous phase) interacting with NH_2-functionalized polymer surfactants (in the nonaqueous phase) [35]. Cai et al. (2017) utilized silica nanoparticles interacting with cationic surfactants such as cetyltrimethylammonium bromide (CTAB) to initiate the bicontinuous stabilization of glycerol and silicone oil [34]. They found that it was important to first mix the liquids slowly (i.e., at 200 rpm, 60 s) and then rapidly for a long time (5 min) to facilitate both the generation of a bicontinuous architecture and particle-stabilized interfaces. Using direct mixing, different biobased oils, and plant-based derivatives, even those with high viscosities can be used to make bijels [54]. For example, homogenization techniques such as simple stirring, vigorous shaking, or rapid mixing of liquids using high shear mixer instruments afford a versatile route to fabricate bijels made with a wide variety of liquid−liquid pairs.

After outlining the methods used to fabricate bijels including significant processes such as thermal quenching, solvent-induced phase separation, and direct mixing, the next section explains the principles of bijel design and the methods used to control their structures toward generating novel materials for a variety of applications.

3. Bijel design and structural control

New types of emulsion- and gel-based biomaterials are needed for broad applications in the bionanotechnology industry based on their structural properties. The process of bijel fabrication is unique, granting features including the reproducible generation of 3D bicontinuous architectures and the ability to control domain sizes at multiple length scales for emulsions and gels [55,56]. By using bijels as templates, macroporous materials with multiple porosities, uniform sizes, or hierarchical structures can be developed [12,57,58]. These structural features unique to bicontinuous structured systems are relevant for varied applications where, for example, controllable channel sizes, different porosities, and permeabilities in porous networks are suitable for efficient cell growth and migration, and transportation of biological entities [59,60].

Moreover, different types of nanoparticles ranging from silica, gold, and graphene oxide can be used to stabilize bicontinuous structured emulsions, gels, and polymer composites

to extend their utility in tissue engineering and other biomaterials applications [7]. To design such bicontinuous systems, including bijels, and to control their morphologies, the following important processing parameters should be considered:

(i) **Route of spinodal decomposition:** This involves making bicontinuous channels with tunable domains based on factors such as selection of critical liquid–liquid compositions, thermal quenching rate, and controlled solvent removal processes [11,12,52]. A combination of spinodal decomposition and nucleation can be derived to form what is known as "bridged bijels" having large-sized and tunable domains [61].

(ii) **Selection of particles and control of particle surface properties:** Selection of a wide range of colloidal particles and tuning their surface chemistries to be made compatible with the bijel-casting formulation [11,12,62]; controlling bijel structures using a varied concentration of colloidal particles, different sizes, and aspect ratios to control bijel domains [62].

(iii) **Utilizing post-processing parameters:** This includes using methods such as selective partitioning of monomeric chemicals into one phase of the bijel and inducing polymerization via photoinitiation, with the ability to control the mechanical properties of final polymers based on factors such as the amount of cross-linker used, cross-linking time, and cross-linking density [12,13,59].

Therefore, based on their tunable micro- and nanostructured properties, bijel fabrication presents a bottom-up approach to design new materials with complex structures for interesting applications in the bionanotechnology industry.

3.1 Controlling the shapes, sizes, and mechanical properties of bijels

Haase et al. (2015) developed a novel method using the solvent transfer approach to make a wide range of bijel materials with different shapes and sizes, expanding their potentials for diverse applications [12,21]. In some cases, bijel structures have been modified into different membrane shapes for applications in wastewater treatment [21] and microfluidic reactors [24]. In a typical example of making hollow fiber membranes using the STrIPS approach, a ternary mixture formulation was extruded through a coaxial microfluidic device concomitantly with a stream of water at the center of the developing bijel scaffold as shown in Fig. 11.4A-i [21]. Simultaneously, the third stream of water was supplied around the bijel jet to form hollow fibers. The more hydrophobic liquid component of the bicontinuous scaffold was endowed with a cross-linkable monomer (e.g., diacrylates) and a photoinitiator to facilitate the formation of a solid bicontinuous network via UV light photopolymerization [12,13].

This approach leads to the development of hollow fiber membranes with high nanoparticle loadings at the bicontinuous interfaces, generating a new type of nanocomposite

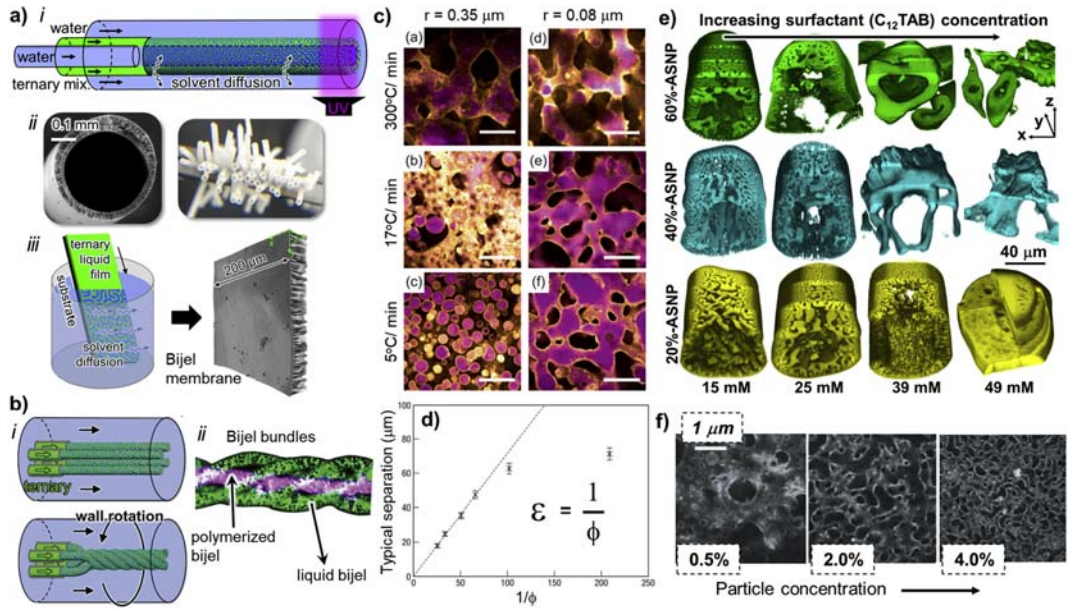

Figure 11.4

Structural control of bijels using tunable fabrication routes. (A) Generation of bijel-based hollow fiber membranes using coaxial microfluidic extrusion of ternary mixtures to form bijels via solvent transfer–induced phase separation (STrIPS). (A-i) Microfluidic extrusion of bijels using coaxial capillaries to generate hollow fiber membranes. (A-ii) Scanning electron micrograph of a bijel hollow fiber cross section (left) and an optical micrograph of multiple bijel fibers. (A-iii) Development of planar bijel membranes by initiating STrIPS on a thin film. (B) Making bijel bundles and ropes by microfluidic twisting to develop high tensile strength materials. (C) Control of bijel domain sizes and structures by varying particle sizes and thermal quenching rate. (D) Effect of spherical particle concentration on bijel domain sizes showing increasing domain sizes with decreasing particle concentration. (E) Control of bijel structures via hydrophobic functionalization and in situ modification of particles via surfactant interactions. (F) Effect of particle volume fractions on bijel domain sizes formed by the thermal quenching method using water and 2,6-lutidine as the biphasic liquids. *From (A-ii) Copyright 2017, Nature materials, M.F. Haase, H. Jeon, N. Hough, J.H. Kim, K.J. Stebe, D. Lee, Multifunctional nanocomposite hollow fiber membranes by solvent transfer induced phase separation, Nat. Commun. 8 (1) (2017) 1234. 10.1038/s41467-017-01409-3; (A-iii) Copyright 2010, M.F. Haase, K.J. Stebe, D. Lee, Microparticles: continuous fabrication of hierarchical and asymmetric bijel microparticles, fibers, and membranes by solvent transfer-induced phase separation (STRIPS), Adv. Mater. 27 (44) (2015) 7065–7071. 10.1002/adma.201570297; (B) Copyright, 2010, S.P. Kharal, R.P. Hesketh, M.F. Haase, High-tensile strength, composite bijels through microfluidic twisting, Adv. Funct. Mater. (2020). 10.1002/adfm.202003555; (C) Copyright 2015, M. Reeves, A.T. Brown, A.B. Schofield, M.E. Cates, J.H.J. Thijssen, Particle-size effects in the formation of bicontinuous Pickering emulsions, Phys. Rev. E 92 (3) (2015) 032308, 10.1103/PhysRevE.92.032308; (D and F) Copyright 2007, E.M. Herzig, K.A. White, A.B. Schofield, W.C.K. Poon, P.S. Clegg, Bicontinuous emulsions stabilized solely by colloidal particles, Nat. Mater. (2007). 10.1038/nmat2055; (E) Copyright 2019, S. Boakye-Ansah, M.S. Schwenger, M.F. Haase, Designing bijels formed by solvent transfer induced phase separation with functional nanoparticles, Soft Matter 15 (16) (2019) 3379–3388. 10.1039/c9sm00289h.*

membrane with synergistic properties derived from the nanoparticles and polymers as shown in Fig. 11.4A-ii [21]. This feature is relevant for a wide range of bionanotechnology applications such as antimicrobial uses in biomedicine, photocatalysis in chemical technologies, and adsorption processes in environmental remediation. Also, bijel-based planar membranes can be derived by simply coating a solid substrate with a thin film of the ternary mixture as shown in Fig. 11.4A-iii [12]. When the thin film is introduced into water, the solvent within the ternary mixture diffuses into the surrounding water to develop flat membranes with bicontinuous nanoparticle-reinforced interfaces suitable for filtration and adsorption applications.

To further extend the types of membrane materials developed from STrIPS bijels, Kharal et al. (2020) have used a microfluidic twisting approach to develop bijel bundles and ropes with significantly improved tensile strength properties compared with their single fiber counterparts [42]. Continuous bijel fiber bundles were produced using hydrodynamic twisting, which involves manipulating the rotational and translational shear stresses derived from the external continuous water stream as shown in Fig. 11.4B. This approach is suitable to be extended, not only in bijel composite materials, but also in reconfigurable printed liquids, complex-shaped hydrogels, capillary suspensions, and high-internal phase emulsions. By selective polymerization of one or more of the bijel fibers, high-tensile-strength composite bijel bundles were generated to promote robust applications in microfluidic transport and catalysis. In this scenario, the authors used different compositions of the initial bijel casting formulation flown in different microfluidic channels, enabling the polymerization of a central bijel fiber and the preservation of the liquid domains in surrounding fibers. Apart from manipulating the bulk structures of bijel materials with different shapes and sizes, the internal bicontinuous liquid domains can be modified, adding to their overall structural tunability at multiple length scales.

Reeves et al. (2015) investigated the factors controlling bijel domain structures and realized that not only is the wettability of colloidal particles important to determine the formation of bicontinuous structures, but also the rate of thermal quenching determines the structural integrity of bijel materials [63]. Two particles with different sizes were used, and by approaching thermal quenching at different heating rates, they realized that smaller-sized particles were more preferred. This was needed to make more versatile bijels as shown in Fig. 11.4C. Spherical particles with a radius of 80 nm were used in the bijel fabrication protocol. A wide range of thermal quenching rates, as low as 5°C/min and as high as 300 °C/min, were used to generate bicontinuous networks. On the other hand, bigger particles (350 nm) were only limited to more rapid quenching rates. In all cases of using varying sizes of particles, phase inversion occurs when the particle contact angle deviates extremely from the near-neutral wettability condition. For example, O/W

emulsions convert to W/O emulsions when the hydrophobicity of the particles is increased via surface modifications. It, therefore, becomes essential to carefully control the contact angles of colloidal particles used in bijel generation irrespective of the approach used.

Herzig et al. (2007) formed bijels using spherical silica particles with volume fractions between 0.5% and 4.0%, via the thermal quenching approach by warming a critical mixture of 2,6-lutidine and water to 40°C at a rate of $17^{o}Cmin^{-1}$. Increasing the particle volume fraction resulted in decreased bijel domain sizes, due to the early interfacial arrest of spinodal phase separation since more particles were available to populate the newly formed bicontinuous interphases. Moreover, bijels are formed with characteristic domain sizes (ε) having the relationship, $\varepsilon = r/\theta$, and depending on the radius (r) and concentration of the particles (θ) [11]. When the same volume fractions of particles are used, smaller-sized particles result in the early-stage interfacial arrest of bicontinuous structures, possibly due to the high mobility of small-sized particles. Hence, by using relatively smaller-sized (67 nm) silica nanoparticles, Tavacoli et al. (2011) realized a significantly small domain separation ($\varepsilon = 2.4$ um), realizing the unique advantage of developing bijels with high interfacial areas [27]. This feature will preferably increase the performance of bijel-based materials in applications such as drug delivery and biphasic reactions, where properties such as increased solubilization of chemical and biological entities, efficient transport, and separations can be realized. Another interesting feature of the effect of colloidal self-assembly in bijel formation is the aspect ratio of particles. Hijnen and coworkers (2015) showed the use of rod-shaped particles to make bijels [64]. As compared with spherical particles, rod-shaped particles caused a significant decrease in domain sizes with increasing particle concentration due to the orientation of the rods at the bicontinuous interphases. This means that several opportunities exist to explore the structural formation of bijels using more exotic particles.

Furthermore, the microstructural properties of bijels using careful control of particle contact angles via in situ surfactant modification have been developed via the STrIPS method. Boakye-Ansah et al. (2019) showed that increasing the hydrophobicity of silica nanoparticles by attaching hydrophobic functional groups enabled the formation of bijels at relatively low surfactant concentrations compared with higher concentrations used for pristine silica [25]. In certain cases, no surfactants were used, and particles formed bijels based on their inherent hydrophobicity via functionalization with hydrophobic organosilanes. Upon realizing that higher degrees of hydrophobic functionalization required fewer surfactant concentrations, a case was made that the initial wettability of the particles determined the extra concentration of surfactants needed to stabilize bicontinuous structures [25,41]. A wide range of gel-based bionanotechnology applications can be derived by carefully controlling the sizes and shapes of nano- and microstructured materials.

Jansen et al. (2011) also showed via simulations that colloidal particles with "off-neutral wetting" can form bijels for different solvent ratios, demonstrating that rapid transitions can be made from bijels to discrete Pickering emulsions, based on the contact angle (θ), the particle concentration, and the ratio of the solvents [65]. Witt et al. (2013) also made mechanically robust bijels with tunable domain sizes via reinforcing one of the continuous domains with a network of colloid-bridged droplets, with a dual morphology resulting from combined spinodal decomposition and nucleation and growth in a binary liquid mixture. The mixture contained colloidal particles with off-neutral wetting properties and partial affinity for one liquid phase [61]. Large domain sizes ($\varepsilon = 400$ um) were recorded and were attributed to colloidal partitioning between the spinodal surface and the fluid domains, causing a delay in structural arrest. The discussed parameters are key modifications of bijels, and in developing new materials for the bionanotechnology industry, considerations must be made on how to effectively incorporate biological entities without deteriorating their structural integrity.

4. Effect of biological entities in the fabrication, design and structural control of bijels

Adding biological components into bijel fabrication protocols has the potential to foster the development of new and interesting nano- and microstructured materials for groundbreaking applications in the bionanotechnology industry [66]. This possibility is based on the high potential to use phase separation dynamics—a major step used in bijel fabrication—to compartmentalize a wide range of biological molecules [67]. Additionally, complex structures can be obtained via the biphasic separation of microbial particles [68], for uses within the food industry [69]. Liquid−liquid separation also presents an important method used in biological and chemical processes to selectively partition and distribute biomolecules between two immiscible fluids. In handling biological entities such as cells and organelles, it is important to pay close attention to the properties of the phase-separated components, so that fragile biological components are not destroyed with the loss of biological activity. Hence, in most biologically relevant phase separation systems, two dissimilar aqueous phases are used, to represent the natural environment more compatible with biological entities including biogenic particles and biomacromolecules [68].

Like bijels with an interfacially trapped particle network, nanoparticle-reinforced gels are made by using combinations of networked hydrogels or organogels with nanoparticles (e.g., metallic, nonmetallic, and polymeric particles) relevant in multiple applications such as biosensing, pharmaceuticals, medical, and environmental remediation [70]. The use of particles enables the originally fragile gels and emulsions to be imparted with more robust properties. Additionally, the fluid components allow for uses including encapsulation and

release of active ingredients, and as transportation channels for different biomedical applications including screening, detection, cell delivery, and conduction of ions and macromolecules [71]. Here, the bijels are highlighted as an emerging class of soft materials for new applications in the bionanotechnology industry. Most importantly, the controlled alignment of nanoparticles at the bicontinuous liquid−liquid interfaces of bijels significantly limits nanoparticle aggregation mostly encountered in materials made with both particles and gels.

To add biological macromolecules such as proteins, nucleic acids, carbohydrates, and lipids to the liquid components of bijels, it will be important to evaluate their effects on fabrication parameters such as spinodal phase separation, speed of particle migration during the coarsening process, and the integrity of interfacial attachment with particles. This will be important in methods such as thermal quenching [11] and phase separation via solvent transfer [12]. Alternative methods such as direct mixing of the biphasic liquids might be more suitable to form bijels in cases where the biological liquid pairs are difficult to mix or to undergo spinodal phase separation [37]. However, more research in this growing field is needed. Otherwise, the bijel framework could be formed using commonly used liquids, following which the biological ingredients may be introduced based on their solubility and partitioning behavior into the dissimilar liquid phases (e.g., oil and water).

An example of this phenomenon is what Rousseau et al. (2015) demonstrated in using microbial cells to stabilize bijels made of phase-separated gelatin−maltodextrin [32]. The microbial cells, namely, *Saccharomyces cerevisiae* (yeast), *Lactobacillus bulgaricus* (an intestinal bacteria), and *spirulina* (edible cyanobacteria), preferentially partitioned into the gelatin (protein) phase and also adsorbed on the bicontinuous interfaces to stabilize bijels for several months as shown in Fig. 11.5A−C. Without the presence of microbes, droplet-type gels formed due to lack of interfacial arrest during spinodal phase separation as shown in Fig. 11.5D.

This approach can be used to integrate different microbial cells into bijels for diverse bionanotechnology applications in foods, environmental remediation, and biphasic chemical reactions. Later, the use of bijels as biphasic media for enzymatic reactive separations and high-yield chemical reactions will be discussed. Another interesting feature in adapting bijels for bionanotechnology applications is to use microgels as interfacial stabilizers [72]. Microgels respond faster to environmental changes than bulk particles and are more suitable for medical biosensor applications [73]. Moreover, microgels have a higher interfacial area per unit mass granting high exchange rates of chemical and biological substances [74]. Based on the compatibility of most microgels with several biological entities, they can be used for multifunctional purposes such as hosting active chemical or biological ingredients in the microgel particle network, at the

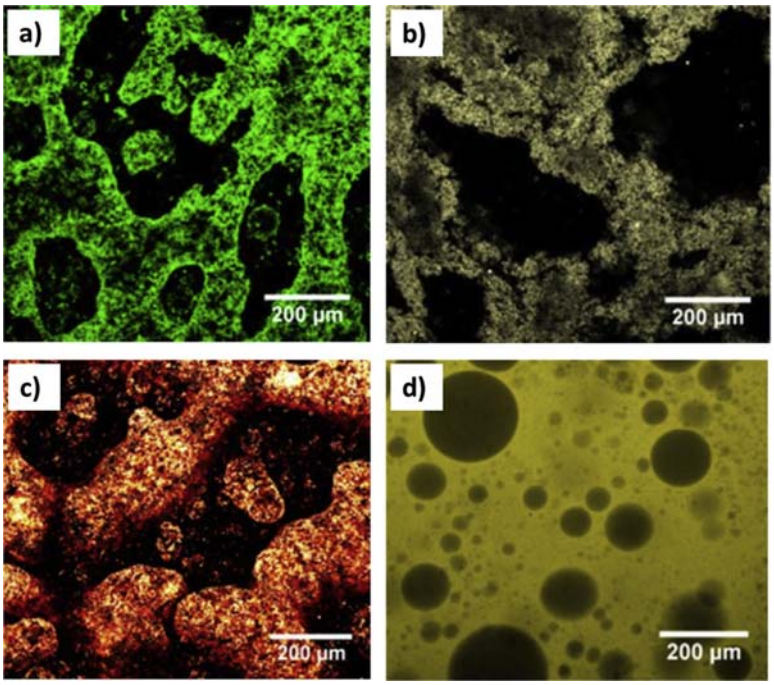

Figure 11.5

Use of biological entities to fabricate bijels made up of a protein–polysaccharide bicontinuous scaffold stabilized with (A) spirulina, (B) *Lactobacillus bulgaricus*, and (C) yeast cells. (D) Formed droplet-based emulsions (control experiment) due to the absence of microbes to stabilize phase separation. *From Copyright, H. Firoozmand, D. Rousseau, Food-grade bijels based on gelatin-maltodextrin-microbial cell composites, Food Hydrocolloids 48 (2015) 208–212, 10.1016/j.foodhyd.2015.02.034.*

same time, serving as interfacial stabilizers. This approach enhances the encapsulation of active ingredients (e.g., drugs and detector chemicals) into microgels. Controlled release of active ingredients into the bicontinuous liquid–liquid networks can be realized by stimuli-responsive functions, presenting a fascinating approach for stimuli-responsive applications in the bionanotechnology industry. In cases where microgels may be too soft and might inhibit efficient attachment to bijel interfaces, fractional volumes of harder particles (e.g., silica, alumina, and gold) may be combined with microgels to give more robust features in the overall bijel structure [75]. More highlights on different factors to be considered when integrating biological systems in bijels are later presented in the section on conclusion and future perspectives. For more insights on the use of biological entities to make bijels, interested readers are referred to the publication titled, "Bijel systems based on the phase separation of biological macromolecules" [66] for more insights into the topic. In the next section, more explanation is provided for the benefits of bijels in distinct applications, focusing on how the bicontinuous morphologies afford unique properties for the bionanotechnology industry.

5. Applications of bijels

In the past, particle-stabilized emulsions have been used to develop new and interesting materials in diverse fields such as healthcare, pharmaceuticals, biomedicine, environmental remediation, and agriculture [4,76]. Their liquid–liquid phases could possess essential components and active ingredients that may supply useful purposes unique to the mentioned applications. A review of the different fabrication methods of bijels, their processing parameters, and applications is summarized in Table 11.1. In addition, the interfacially trapped particles provide mechanical robustness to gels and emulsions structures. The use of bijels means that not only are the biphasic liquid components accessible for interface exchange and mass transfer for controlled release systems, but also their large interfacial areas are desired for important applications including biphasic catalysis, filtration, and adsorption [21,24].

This unique feature in bijels adds significantly improved benefits in applications involving emulsions and gels such as (1) high yields in biphasic reactions, (2) high adsorbent surface area for efficient filtration and purification, (3) large interfacial area for mass transport and exchange of chemicals or biological components for drug deliveries, and (4) efficient transport characteristics relevant in, for example, energy storage and tissue engineering applications. In this section, we highlight the significance of bijel structures and novel methods used in their postprocessing, which has helped to generate new materials for different applications of interest to the bionanotechnology industry.

5.1 Accessing the liquid domains of bijels for different applications

Generally, liquid–liquid emulsions stabilized at the interface with colloidal particles offer unique advantages to develop structured micro- and nanomaterials for applications in industries spanning healthcare, food, pharmaceutical, agriculture, and energy [4,22]. Principally, what makes emulsions desirable for the listed purposes include their unique features such as biphasic transport, encapsulation and release, and interfacial mass exchange. Particle-stabilized emulsions impart additional features such as high mechanical robustness, high porosity, large and tunable interfacial area, controllable permeability, and percolating channels of the constituent materials, relevant for applications including separations, biphasic catalysis, controlled drug delivery, and enhanced cell delivery. In this section, the unique advantages of bijels as particle-stabilized emulsions for liquid-based applications are discussed, with emphasis on the enhanced performance of bicontinuous networks in the respective applications.

Table 11.1: Principles of bijel formation and their applications.

Method		Bicontinuous interface generation	Particle properties	Morphology	Particle wettability control	Postprocessing and applications	References
Thermal quenching	UCST	Spinodal decomposition by cooling immiscible liquids (e.g., nitromethane and ethylene glycol) to room temperature	Silica particles with sizes 67—450 nm, and volume concentrations ranging 4%—11.5%.	Bicontinuous emulsions are stable at room temperature with domain sizes 2—100 mm. Increasing particle concentration results in smaller domain sizes	Silanization of particles with hydrophobic functional groups	Bijels with high surface area for biphasic chemical reactions, general porous solid scaffolds, drug delivery, tissue engineering, and stimuli-responsive emulsions for controlled release	[27,52,58,62,66,77]
	LCST	Spinodal decomposition by heating immiscible liquids (e.g., 2,6 lutidine and water) above ~34 °C	Silica particles with 100—500 nm sizes, and volume concentrations ranging 1%—1.5%.	Bicontinuous emulsions with domain size 20—100 mm. Fully penetrating, nonconstricting pores	Varying drying time and temperature control of particles	Polymerization of the liquid phase to create porous scaffolds for tissue engineering including bioimplants with enhanced tissue integration. Porous monoliths and templates for high energy density electrodes	[11,13,56,58,59,63,78]
Solvent transfer	STrIPS	Spinodal decomposition of phase-separating immiscible liquids by	20—100 nm silica particles with concentrations 1%—30% (mass). A	500 nm to 2° mm domain sizes. Long fibers with hierarchical porous	Surfactant adsorption silanization Use of a fraction of	Continuous fabrication of bijel-based porous fibers, hollow membranes, twisted bundles,	[12,19,24,25,41,44]

		solvent removal in a ternary mixture (e.g., HDA monomer, water, and ethanol)	mixture of hydrophilic and hydrophobic nanoparticles 1%–14% (mass).	networks, hollow fibers, twisted fiber bundles, elongated particles, spherical capsules, and planar sheets	hydrophilic nanoparticles	catalytic reactors, drug-delivery, filtration, and water purification Postprocessing via silica precipitation to generate robust scaffolds	
	VIPS	Spinodal decomposition, nucleation, and growth by applying a ternary mixture as a thin film on a flat substrate and inducing cosolvent removal via airflow at ambient conditions	Silica nanoparticles with size, 20 nm, and loaded at 9% (vol) in the ternary mixture	5–20 mm liquid–liquid domains with controllable sizes. Increasing solvent evaporation rate by rapid airflow results in smaller domain sizes. Varying oil/water ratio or quenching rate to control domain sizes. Secondary-phase separation to produce hierarchical structure-in-structure features	Surfactant adsorption on silica nanoparticles	Polymerization of monomer oil phase to form thin-film membranes. Scalable manufacturing of films under ambient conditions. Encapsulation and release of active ingredients. Versatile development of functional coatings, skincare/homecare products. Biphasic liquid or solid composites for filtration and catalysis	[79]
Direct mixing	Single or double	Shear stress via mechanical stirring.	Silica nanoparticles with sizes ranging from	500 nm–10 um domains, nonuniform sizes. Increasing	Surfactant adsorption, polymer nanoparticles	Potential applications in multiphase microreactors,	[34,35]

Continued

Table 11.1: Principles of bijel formation and their applications.—cont'd

Method	Bicontinuous interface generation	Particle properties	Morphology	Particle wettability control	Postprocessing and applications	References
step mixing		14 to 65 nm. Particle concentrations at 0.05%–2.5% (mass)	concentration of functional polymers and particles to drive smallest length scales		microfluidic devices, membrane contactors, and multiscale porous materials. Stimuli-responsive nanoparticle surfactants to develop reconfigurable liquid bicontinuous systems with reconfigurability to external fields	
Others	Phase inversion of emulsions via particle modification	Stober synthesized silica particles with increasing hydrophobicity of particles via	345–428 nm particles. O/W to W/O emulsions with bicontinuous emulsion formation at inversion	Hydration of particle surface Silanization. Varying the temperature or duration of drying step	Drug delivery, gel-based uses for corelease and coflow, porous medium, tissue scaffolds	[40]

HDA, 1,6-hexanediol diacrylate; *LCST*, lower critical solution temperature; *STrIPS*, solvent transfer–induced phase separation; *UCST*, upper critical solution temperature; *VIPS*, vapor-induced phase separation.

5.1.1 Drug delivery

The recent global pandemics, chronic diseases, and different forms of cancer have increased the global demand for new and efficient drug delivery and diagnostic systems [80]. Lipid-based formulations including particle-stabilized emulsions made with oil and water offer unique advantages such as enhanced lipophilic drug solubilization, increased bioavailability, enhanced delivery, and efficient absorption into biological tissues [81]. This approach enables the development of highly potent, but poorly water-soluble drug candidates that can be encapsulated in biphasic microemulsions having lipophilic and hydrophilic domains [82,83]. Moreover, a wide range of drug molecules (in both hydrophilic and hydrophobic forms) can be encapsulated and released on demand, by using lipophilic excipients for topical delivery, controlled release, and target delivery applications [82]. By using Pickering emulsions for drug delivery applications, key features such as high stability against coalescence, improved mechanical robustness, and high biocompatibility would be obtained. Moreover, solid particles endow emulsions with useful characteristics such as conductivity, stimuli-responsiveness, and high porosity, further expanding their potential applications in energy and biomedicine [4].

The invention of bijels opens new doors for Pickering emulsion systems, providing enhanced performances in applications involving encapsulation, interfacial exchange, mass transport, and drug release [24,27]. The unique bicontinuous architecture of bijels contributes to the efficient exchange of chemical substances between the polar and apolar phases. Moreover, the biphasic constituents in bijels may comprise aqueous solutions of macromolecules or polymer blends, which have been significantly applied in several areas such as polymer drugs, self-assemblies, implantable materials, and controlled drug release [84,85]. Low-molecular-weight drugs bound to other enzymes and transport proteins can be loaded into the oil domains of bijels. Great benefits in drug delivery applications can be derived from the high interfacial area available in bijels for the efficient exchange of molecular species.

Furthermore, the interfacial stabilizers in bijels can be made of nanoparticles relevant for drug or gene delivery applications, such as (1) natural materials or their derivatives, including chitosan, dextran, gelatin, starch, and liposomes, (2) polymer carriers including polylactic acids, polyethyleneimines, and polycaprolactones, (3) dendrimers including branched polymers, and (4) fullerenes such as carbon-based carriers [86]. Furthermore, the unique potential of bijels offers in drug deliveries. Clegg et al. (2011) has demonstrated the fabrication of novel, robust, and versatile bijels with sub-10-micrometer domains [27]. Fig. 11.6 shows an example of a bijel capsule having a 3D structure observed by confocal laser scanning microscopy images at different depths into the capsule. The contained liquid materials are released based on either temperature changes or the addition of a solvent as shown in Fig. 11.6B, demonstrating how bijels can be applied for stimuli-responsive drug delivery applications.

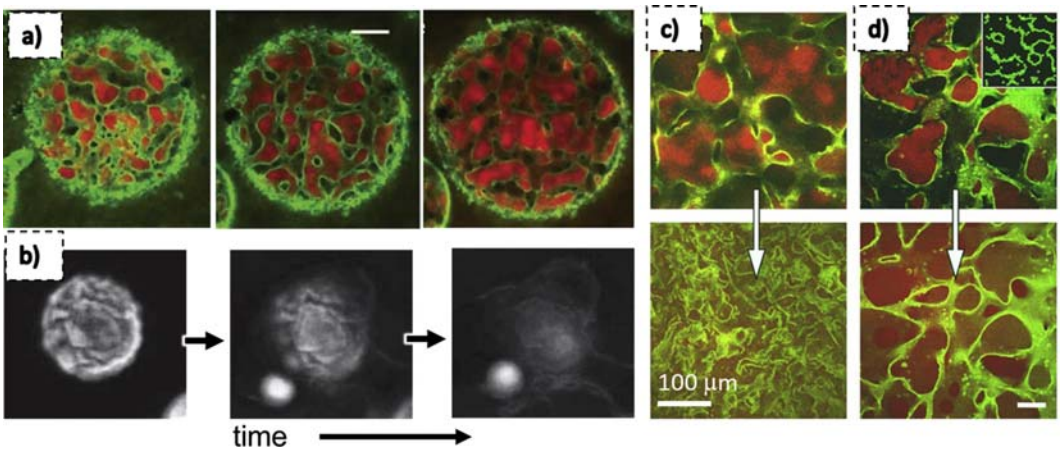

Figure 11.6

Tailoring bijels for encapsulation and release applications based on their liquid–liquid domains. (A) Fluorescent confocal stacks of a bijel capsule with fluorescent nanoparticles at the bicontinuous interfaces. From left to right, images are 10 mm apart. (B) Bulk release of encapsulated materials in the bijel capsule based on a stimuli-responsive approach. (C) Deformation of bijel structure after remixing of liquid components due to removal of interfacial tension. (D) More robust bijels with stable particle network after removal of liquids, more suitable for recyclable encapsulation and release applications. *(B) From Copyright, J.W. Tavacoli, J.H.J. Thijssen, A.B. Schofield, P.S. Clegg, Novel, robust, and versatile bijels of nitromethane, ethanediol, and colloidal silica: capsules, sub-ten-micrometer domains, and mechanical properties, Adv. Funct. Mater. 21 (11) (2011) 2020–2027, 10.1002/adfm.201002562; (D) Copyright, E. Sanz, K.A. White, P.S. Clegg, M.E. Cates, Colloidal gels assembled via a temporary interfacial scaffold, Phys. Rev. Lett. (2009), 10.1103/PhysRevLett.103.255502.*

When the liquid components are released from the bulk structure in bijels, the bicontinuous structure would most often collapse due to the removal of the interfacial tension. The colloidal monolayer templating the bijel structure follows in collapsing to create a deformed structure as shown in Fig. 11.6C. To reuse bijel capsules in applications where the liquid components are removed, the bicontinuous arrangement of colloidal particles must remain in place even after the liquids are mixed. Cates et al. (2009) demonstrated this potential by forming more robust and stable bijels. The colloidal network remains intact on the bicontinuous interfaces after remixing the liquids as shown in Fig. 11.6D [87]. This stable phenomenon was attributed to the presence of attractive interactions, where the particles were maintained in a primary minimum Derjaguin–Landau–Verweg–Overbeek (DVLO) bonds [78]. This robust property in bijels is needed, especially in recyclable drug delivery applications, where the chemical and biological components can be loaded, offloaded, reloaded, and offloaded again [88]. In the next section, the important feature of having more robust bijels with stable interfacial properties is introduced as highly relevant in biphasic chemical separations, transport, and reactions.

5.2 Biphasic reactive separations

Biphasic chemical reactors made of particle-stabilized emulsions have recently piqued the interest of scientists based on the use of solvent-free systems in chemical reactions, transport, and separation of chemicals [89,90]. Hence, biphasic reactor methods such as Pickering interfacial catalysis have been significantly investigated, with the high potential to enhance the production of fine chemicals using a green chemistry approach [90]. However, with the use of droplet-based Pickering emulsions in chemical synthesis, the reactor and products must be restocked and separated, which can be very tedious and prohibiting continuous processing [90–92]. Moreover, the strong attachment of colloidal particles at liquid–liquid interfaces present limitations such as difficulties in breaking up emulsions and forming them again to either replenish reactor chemicals or recover phase-separated products in multistep batch processes. On the other hand, using bijels, chemical reagents can be added through one phase, undergo reaction and conversion at the interface, and subsequently partition to the other phase as shown in Fig. 11.7A-i. Also, the interpenetrating domains of the biphasic liquids stabilized at the bicontinuous interface with colloids present a high surface area platform for intimate contact between the liquid–liquid phases as shown in Fig. 11.7A-ii.

Cha et al. (2019) used bijels generated by the STrIPS method for enzymatic reactive separations [24]. Bijel fibers were generated via microfluidic extrusion of a ternary mixture made up of water, diethyl phthalate, and a cosolvent, ethanol. Silica particles interacted with cationic surfactants to generate bicontinuous structures with long-term stabilities. Fig. 11.7B shows an example of the model used, where lipase-catalyzed hydrolysis of tributyrin was performed in this reaction step. Tributyrin was introduced into the hydrophobic (oil) phase, which was partitioned into the more hydrophilic phase initiating catalysis by the enzyme, lipase, resulting in the higher yield production of glycerol. Due to the high surface area of the bicontinuous architecture, as exemplified in Fig. 11.7C-i, the reaction rate of the chemical process increased fourfold, as opposed to a low yield output in the emulsion-based droplets, which is shown in Fig. 11.7C-ii. Bijels, therefore, provide a powerful biphasic reactor platform for advancing chemical reaction processes to efficiently perform biphasic chemical reactions in a solvent-free and environmentally friendly manner. Moreover, novel particle reinforcement techniques can be used to adapt bijels for harsh chemical reactions involving drastic pH changes and temperature spikes, relevant in applications such as homogeneous catalysis [19,25].

5.3 Food applications

The use of bijels as food-based systems is still escalating, with the potential to be beneficial as food-grade macromolecules and natural biopolymers including proteins,

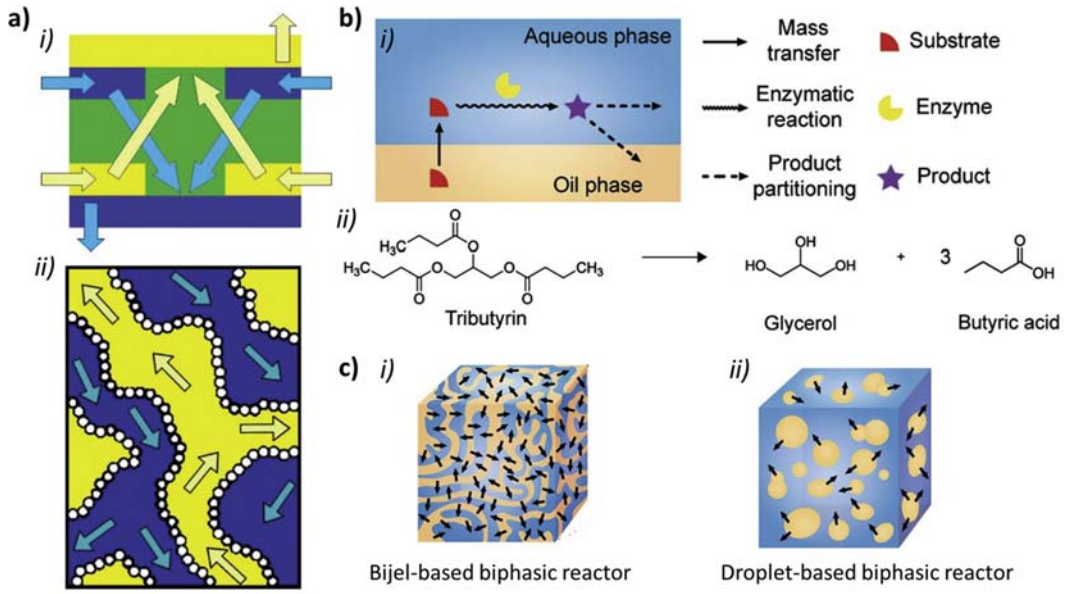

Figure 11.7

Biphasic reactive separations in bijels. (A) Schematic illustration of the use of bicontinuous scaffolds for continuous cross-flow microreactions, where (i) reactants and products are supplied and removed simultaneously and (ii) biphasic liquids and their chemical ingredients have intimate contacts at the percolating particle scaffold. (B) Schematic illustration of a biphasic system where a hydrophobic substrate (tributyrin) and a hydrophilic enzyme exist in the oil and water phases, respectively. Mass transfer of the substrate to the aqueous phase is followed by enzymatic reactions to yield products that partition into either the oil or aqueous phase. (ii) Chemical reaction used in the bijel reaction model. (C) Comparison of a bijel-based reactor with a high interfacial area with a droplet-based reactor with a limited interfacial area to depict the advantages of bicontinuous interfaces in biphasic reactions. *(A) From Copyright, M.E. Cates, P.S. Clegg, Bijels: a new class of soft materials, Soft Matter 2008. 10.1039/b807312k; (C) Copyright, S. Cha, H.G. Lim, M.F. Haase, K.J. Stebe, G.Y. Jung, D. Lee, Bicontinuous interfacially jammed emulsion gels (bijels) as media for enabling enzymatic reactive separation of a highly water insoluble substrate, Sci. Rep. 9 (1) (2019). 10.1038/s41598-019-42769-8.*

carbohydrates, and polysaccharides as the biphasic liquid components, as well as the use of digestible particles as interfacial stabilizers [32]. For the first time, Rousseau et al. (2015) demonstrated the generation of food-grade bijels by using inactivated single-celled microorganisms to stabilize bicontinuous gels made up of gelatin and maltodextrin, shown previously in Fig. 11.5. The microbial cells, including bacteria and yeast species, acted as interfacial stabilizers keeping the bijels for several months. This scope of research can be extended to other types of food-grade nanoparticles, which are made of organic or inorganic materials composed of silver, iron oxide, titanium oxide, silicon dioxide, or zinc oxide, to be integrated into bijel systems [93,94]. A wide range of nanoparticles with the

potential to be used as bijel stabilizers would provide useful benefits in food applications such as follows: (1) silver nanoparticles serving as antibacterial agents in foods and packaging materials, (2) zinc oxide (ZnO) nanoparticles as supplementary foods and antimicrobial packaging, (3) iron oxide (Fe_2O_3) nanoparticles as food colorants or sources of bioavailable iron, (4) titanium oxide (TiO_2) nanoparticles giving unique optical properties to foods, and (5) silicon dioxide nanoparticles to enhance food rheology [95,96].

Different organic nanoparticles such as lipids, proteins, and/or carbohydrates can also be used to stabilize bijels having the bicontinuous phases made up of fats, oils, oil-soluble vitamins, confectioneries, flavors, antioxidants, and other food-based bioactive ingredients and nutraceuticals [95,97]. In summary, these ingredients must be edible, giving rise to foods with enhanced textural properties and taste, owing to the encapsulated food ingredients in the cocontinuous liquid phases in bijels.

5.4 Postprocessing bijels into polymeric scaffolds for biomedical applications

5.4.1 Bijels as general porous scaffolds

Porous materials having 3D architectures and tunable features are highly desired in several bionanotechnology applications such as regenerative tissue growth, pharmaceutical drugs and therapeutics, biocompatible prosthesis, bioimaging, and biosensors [59]. Typically, porous polymer monoliths via emulsion templating are developed by solidifying the hydrophobic (oil) phase by, cross-linking the monomeric oil phase into a solid polymer scaffold. The final structure of the polymeric scaffold, therefore, emerges based on the structure of the biphasic emulsion, leading to the generation of general porous materials including polymer beads, polymer fibers, and porous carbon materials [98,99]. For the first time, Mohraz et al. (2010) demonstrated how bijels can be processed into 3D macroporous materials by selectively polymerizing the oil phase in a bicontinuous network matrix generated via arresting spinodal decomposition of water and 2,6-lutidine [13]. This method has been developed further and used to build materials such as (1) hierarchical porous silver monoliths, an example of which is shown in Fig. 11.8A, for applications in energy systems and sensors, (2) macroporous ceramic polymer with different metal (e.g., copper and nickel) coatings as shown in Fig. 11.8B, (3) biocompatible porous scaffolds for tissue engineering, shown in Fig. 11.8C-iv, hollow fiber membranes for water purification and antifouling applications, as shown in Fig. 11.8D.

The ability to control the bulk structures of bijels is based on different methods such as tuning their bulk properties via microfluidics, controlling the liquid–liquid domain sizes by modulating particle components and postprocessing routes including selective removal

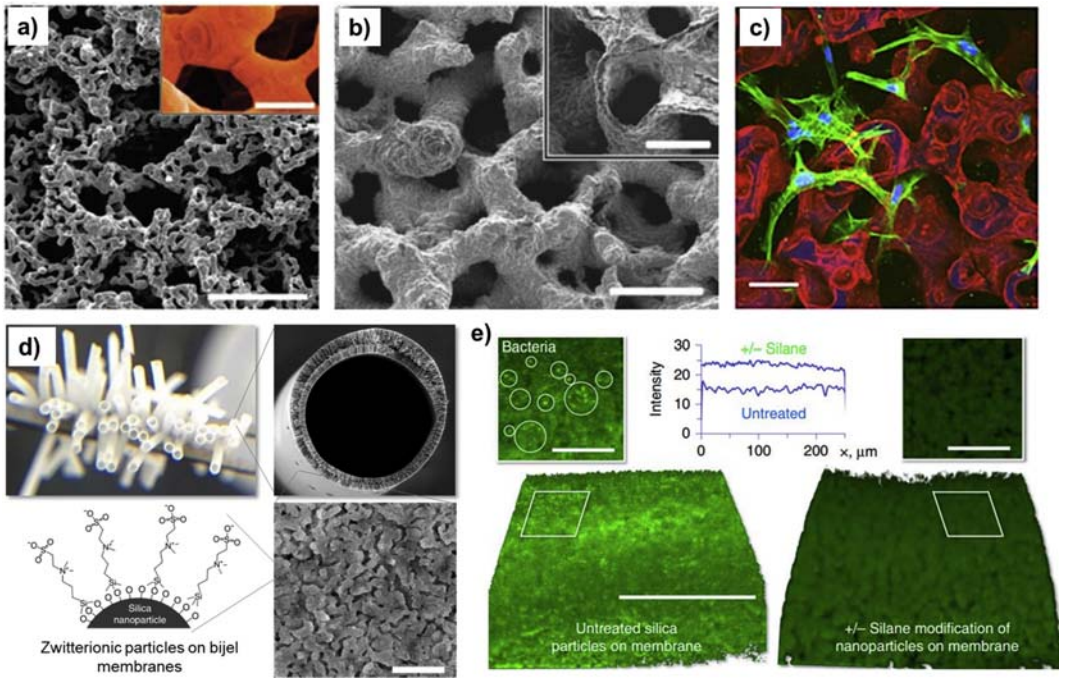

Figure 11.8

Macroporous materials developed from bijels and their uses in different applications. (A) Bicontinuous silver monoliths with hierarchical features suitable for applications such as energy storage materials. (B) Nickel-templated bijel macroporous materials with a shell-like structure suitable for applications requiring properties such as efficient transport and electrochemical processes (C) Composite bijel-templated scaffolds for cell delivery applications. The bijel scaffold is indicated as red, with the network of cell growth (green) in the porous network. (D) Hollow fiber membranes made from bijels suitable for water filtration and purification. (E) Surface modification of nanoparticles with zwitterionic silanes impart bijel membranes with antifouling properties. Surface-modified membranes show strong resistance to bacteria growth as opposed to nonmodified bijels with significant bacteria deposits. *(A) From Copyright, 2011, M.N. Lee, A. Mohraz, Hierarchically porous silver monoliths from colloidal bicontinuous interfacially jammed emulsion gels, J. Am. Chem. Soc. (c. 2011). 10.1021/ja201650z; (B and C) Copyright, 2010, M.N. Lee, A. Mohraz, Bicontinuous macroporous materials from bijel templates, Adv. Mater. 22 (43) (2010) 4836–4841. 10.1002/adma.201001696; (D) Copyright, 2017, M.F. Haase, H. Jeon, N. Hough, J.H. Kim, K.J. Stebe, D. Lee, Multifunctional nanocomposite hollow fiber membranes by solvent transfer induced phase separation, Nat. Commun. 8 (1) (2017) 1234. 10.1038/s41467-017-01409-3.*

of either liquid phases, etching the solid bicontinuous substrate, or colloidal particles to increase their surface area. Hence, bijel design offers several advantages in emulsion-based templating designs. They can be developed into different solid porous materials for a wide range of applications in different fields, including tissue engineering and environmental remediation as discussed in the next section.

5.5 Tissue engineering applications

In nature, materials with bicontinuous networks such as calcareous skeletal elements are desirable to serve as biocompatible platforms for tissue repair and bone regeneration [100]. The bicontinuous framework does not only enable a confluent growth of cellular networks but also facilitates the formation of bridged cells throughout the percolating channels. Bijels presents a new field of developing nonequilibrium materials formed by arresting spinodal phase separation of partially immiscible liquid−liquid mixtures with surface-active particles having phase-neutral wettability. Both fluid phases can be developed for diverse tissue engineering applications [20,26]. Mohraz et al. (2019) have recently developed bijel-templated materials for enhanced tissue integration and vascularization as demonstrated in Fig. 11.9A and B) [26]. They fabricated cylindrical bijel scaffolds and implanted the bicontinuous porous material into the subcutaneous region of mice, also comparing their performance with a typical biomaterial made from a particle-templated scaffold as shown in Fig. 11.9C and D. By analyzing the implant in mice after 4 weeks (Fig. 11.9E), they observed high vascularity, represented by increased sizes of blood vessel sizes and increased amount of healing macrophages in the bijel template as shown in Fig. 11.9B. Contrary to the high tissue integration in the bijel framework, the porous biomaterial made from particle-templated scaffolds exhibited narrow constricted pores with "dead ends" as shown in Fig. 11.9C and D. This resulted in limited sizes of the penetrating blood vessels and stunted cell migration causing macrophage polarization in the particle-templated scaffold. The graph in Fig. 11.9E shows the development of strong tissue response in the bijel-templated scaffold, as opposed to the weak response in particle-templated implants. This performance reaffirms the need for negative Gaussian curvature surfaces, like those in bijel implants, for advanced tissue engineering applications. Therefore, bijel templating could serve as sustainable platforms to generate future biomaterials having tunable surface chemistries, strong bioactive signals, biodegradability, improved functions such as the dense formation of blood vessels, and conducive tissue response features for tissue engineering. In the next sections, bijel materials adapted for membrane filtration and purification are discussed.

5.5.1 Bijel membranes for water filtration, purification, and other applications

Bijels can be modified into polymer filtration membranes for several environmental remediation applications including drinking water purification, gas separations, oil−water separation, and pollutant degradation. The bicontinuous polymer network in bijels provides enhanced features such as high surface area, tunable pore sizes, and membrane toughness for microfiltration, ultrafiltration, or nanofiltration. Haase et al. (2017) have recently developed new multifunctional nanocomposite membranes for water treatment applications by developing highly scalable hollow fiber membranes with a dense layer of nanoparticles at their interfaces to impart useful functionalities [21]. The generated bijel-based hollow

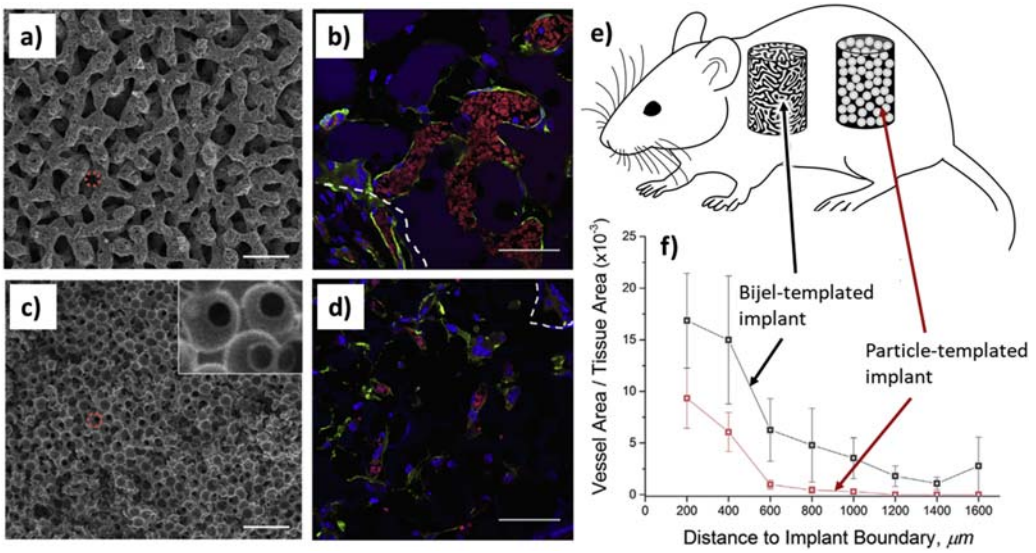

Figure 11.9

Performance of macroporous materials for tissue engineering applications. (A) Image of a bicontinuous scaffold developed by the polymerization of polyethylene glycol diacrylate monomer, constituting the hydrophobic phase of a bijel. (B) Formation of large-sized blood vessels (colored in red) within the bicontinuous network of the bijel-templated material. (C) Image of a typical particle-templated biomaterial having unconnected porous networks. (D) Formation of small-sized blood vessels with stunted cell migration within the narrow and constricted pores of a particle-templated biomaterial. (E) Schematic depiction of mice with different bioimplants in the forms of a bijel-templated or a particle-templated material. (F) Demonstration of high tissue integration in a bijel-templated implant having higher vessel area per mouse, as compared with the low vessel area in a particle-templated implant. *Reproduced from Copyright, 2019, Elsevier, T.J. Thorson, R.E. Gurlin, E.L. Botvinick, A. Mohraz, Bijel-templated implantable biomaterials for enhancing tissue integration and vascularization, Acta Biomater. 94 (2019) 173–182. 10.1016/j.actbio.2019.06.031.*

fibers developed via microfluidic extrusion contained bicontinuous channels having monomers, which were cross-linked via photoinitiated radical polymerization. This approach of using photoinitiated radical polymerization has been used to develop a wide range of bicontinuous macroporous materials from bijel templates [13]. In this water treatment strategy, the bijel-based polymer scaffold was endowed with significantly high nanoparticle loadings. The particles provided the membranes with unique features such as high mechanical strength and controllable membrane pore sizes.

Moreover, the bicontinuous structures imparted the nanocomposite material with high surface area as well as a densely nanoparticle-populated interface distributed over the bulk membrane surface. Based on the ability to modify the surface chemistry of nanoparticles, bijels were endowed with zwitterionic silanes to significantly decrease bacteria adhesion

on the bijel membranes as previously shown in Fig. 11.8D. A wide range of similar zwitterionic agents characterized with positively and negatively charged terminal functional groups are well known for their antifouling capabilities and can be readily used to prevent the buildup of microbial adhesion and biofilm formation [101,102].

This surface modification approach used in bijel synthesis can be extended to several applications such as lithium battery electrolytes, ion exchangers in liquid chromatography, and electrophoresis [103]. Overall, diverse fields such as medicine, pharmaceutical products, food and packaging, aviation, environmental remediation, and the marine industry can greatly benefit from new applications resulting from bijels. In summary, a broad outlook of potential industrial applications of bijels is demonstrated in Fig. 11.10.

6. Conclusion and future perspectives on bijels

In this chapter, work on the various methods used to develop bijels have been discussed and their material properties evaluated for different applications of interest in the bionanotechnology industry. The use of liquid–liquid phase separation techniques including thermal quenching and solvent phase transfer is discussed as important routes to derive bicontinuous interfaces in bijel formation processes. The use of varied types of nanoparticles having different surface chemistries as interfacial stabilizers to design liquid–liquid emulsions into a plethora of complex structures, shapes, and sizes are discussed. Key factors such as particle wettability modifications via covalent attachment of functional groups or in situ surfactant interactions are discussed, with emphasis on the influence of particle surface chemistry on emulsion structures relevant for biomaterials. It is shown that interesting functional properties of bijel nanocomposites can be developed and integrated into a wide range of applications in healthcare, energy, agriculture, pharmaceutical, food, and environmental sustainability.

While the field of bijels shows great promise to impart the future bionanotechnology industry, research efforts are needed to take bijel fabrication from the benchtop to real-world commercial applications. Therefore, scientists working on bijel research need a clear understanding of new growth areas in the industry. This would help to develop new strategies to build industrially relevant bijel materials having high scalability, reproducibility, and affordability. So far, all the bijel synthesis methods ranging from thermal quenching, STrIPS, and direct mixing have shown great promise for practical industrial uses. In particular, the STrIPS method is highly versatile and scalable, which can be used to develop different shapes and sizes of micro- and nanostructured fibers for biphasic catalysis, membranes for wastewater filtration and purification, encapsulation and release materials to apply fertilizers for agricultural purposes, and capsules for drug delivery [9]. In energy research applications, 3D composite electrodes can be developed from bijel materials and used as portable systems for energy storage, reaction conversions

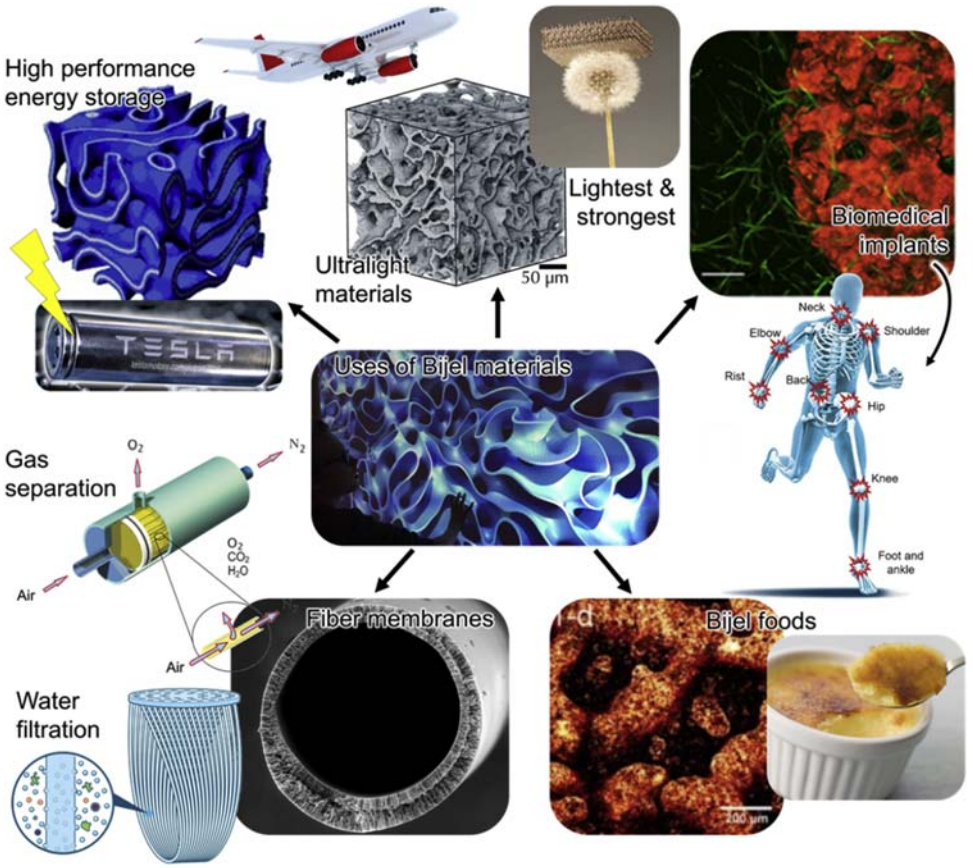

Figure 11.10

Broad outlook highlighting the adaptability of bijels in different fields. Based on their gyroid nano- and macrostructures, bijels can be engineered for uses like high-performance energy storage materials for advanced automation and electric vehicle applications, hollow fiber membranes for gas separation and water filtration, food products having unique textures and tastes, biomedical implants with high tissue integration, and ultralight materials for manufacturing aircraft.

to simultaneously deliver high power and energy densities in biofuel cells [31]. In the automotive industry, unique gyroid morphologies offered by bijel-based electrodes can provide rapid ion transport and high energy storage capacities to develop long-lasting batteries and supercapacitors with ultrafast charge and discharge capabilities for electric vehicles purposes [104,105]. An important part of bijel nanocomposites is their particulate components. Although there are a wide variety of available nanoparticles suitable for important applications in construction, biomedicine, environment, food, and agriculture, the scope of research about integrating nanoparticles into bijel systems is still unexploited [106]. In biological applications, a wide variety of nanoparticles can be integrated into

bijel systems, with those particles serving as core materials with tunable surface properties for uses in a variety of biomedical applications including biorecognition, sensing, delivery, and imaging [107]. Regarding nanoparticles, their reactivity, toughness, and high surface area per unit volumes also make them suitable for integration into both commercial and domestic applications including biphasic catalysis, energy storage materials, environmental remediation, and food technologies. Again, since bijels are predominantly endowed with nanoparticles at their interfaces, an interesting possibility lies in deriving useful bionanotechnology benefits by attaching nucleic acids (e.g., DNA and RNA) with colloidal particles [46,108]. Thus, synergistic properties can be derived from the attached functional groups and a variety of particles in the forms of gold, silica, platinum, and iron.

One area that is strongly lacking in bijel applications is the food industry. Although the structure of bijels can significantly promote the development of new food textures for enhanced mouthfeel, robust scaffolds such as packaging materials, and encapsulation and release gel networks for nutrient supply, there may be problems to integrate necessary biological components into bijel systems. For example, biomolecules are known to interact strongly with colloids, especially, solid particles [109,110]. Amino acids forming proteins could have positive, negative, or neutral charges based on the nature of surrounding fluids [111]. The overall charge of proteins is typically determined by the pH of the surrounding fluids, which will significantly impact the solubility behavior and distribution of protein molecules in the bicontinuous scaffold. Hence, when biological entities such as proteins are used to form bijels, the biomolecules may stick to the nanoparticle interfaces limiting their target release. Moreover, the final morphology of the bulk bijel material will strongly depend on the particle−biomolecule interactions and partitioning behavior of the biomolecules [112].

Lastly, an interesting area for future research into bijel systems is their potential in stimuli-responsive applications [113]. Already, general Pickering emulsions with stimuli-responsive features have received a considerable amount of attention based on their ability to respond to different external triggers such as pH, temperature, CO_2 concentration, light intensity, ionic strength, and magnetic field. In integrating biological systems into bijels, a typical morphological parameter is the ability of proteins to fold and unfold based on the distribution of charges along their molecular backbones [114]. Hence, biomimicking features can be developed by using the stimuli-responsive behavior of biological entities to be used in making bijels. Furthermore, with the ability to design functional particles and use them to fabricate bijels, new and interesting applications can be extended to fields such as enhanced oil recovery, catalysis, cosmetics, and controlled release. In the future, desirable applications including biosensing, biolabeling, cell delivery, diagnostics, and bioelectronics can be developed using bijel structures made with these biological entities. It is possible that in the future, significant progress will be made in taking bijels from the benchtop to useful industrial products.

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CHAPTER 12

A revolutionary breakthrough of bionanomaterials in tissue engineering and regenerative medicine

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1. Introduction

Materials engineering is a collective science hybridizing chemistry, physics, metallurgy, ceramics, and solid state. It is the first example of an innovative academic field emerging from fusion rather than fission [1]. When a material is associated with a biological entity or a moiety for medical applications, it is regarded as biomaterials. There are large varieties of biomaterials covering and envisaging the elements of fields such as medicine, biology, chemistry, tissue engineering, and so on. The understanding principle, mechanism, and application of biomaterials are collectively termed as biomedical engineering or biomedical sciences. Materials exhibiting the size less than 100 nm in thickness are typically classified under the scale of nanomaterials. Since the past decade, the field has been emerging and growing rapidly with advanced research and translational applications, particularly in the meadow of medical health sciences. The shape and size of nanomaterials determine the properties and make them specific for definite rationale such

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as agent for intervention or drug delivery, biosensing of the specific ligand moiety, and engineering cellular structure for advanced-level components or applications, which can be utilized in regenerative medicine. However, the thickness up to 100 nm establishes the concept of the quantum regime, wherein the properties of the material were greatly affected by the quantum effect. As dimension or the size of particles decreases, the phenomenon of the quantum effect also increases [2], and it is because of the confinement of electrons within the particles of dimension smaller than their bulky counterpart [3]. The collective framework of the functioning of cells, scaffolds, and growth factors to regenerate or replace the damaged or injured body part or tissue comes under the idiom tissue engineering (TE). While the same is coupled or used with another strategy, including cell based therapy, gene therapy and immune modulation to make in vivo tissue or organs lead to the concept of regenerative medicine (RM) [4–7].

In the recent past, tissue engineering for regenerative medicine is the most outstanding achievement in biomedical research, seeing that humans and animals may lose tissue or organs by virtue of accident, trauma, disease, and congenital defects. It is well known that the human body has diminutive regeneration potential as compared with the Urodele amphibians (caudate amphibian) commonly known as salamanders. If an organ or tissue can be replaced successfully on demand basis, then the millions of human beings may be benefited. However, regenerative property has been achieved by engineering the cells, tissue with or without supportive material.

Globally, the shortage of tissue and organs has been recognized as one of the major concerns as an important medical health challenge [8], wherein a fraction of the recipients are receiving organs and tissue contrary to top priority lifesaving procedures. For example, one-third of the recipients with heart or liver failure die in the United States alone, before organ transplantation, and approximately 30,000 amputations take place each year in the United States, in case of traumatic injuries, where over two-thirds are young adults and children. In United States alone in the year 2020, there was more than 900,000 survivors post traumatic amputation [9]. Moreover, several companies are also working actively on bioprinted products for tissue engineering application to support the shortage of organs, such as heart, lung, or liver for transplantation [10]. Currently, regenerative medicine has advanced significantly, and various body organs such as heart, liver, skin, and kidney are being routinely transplanted, and regenerative medicine practice to correct congenital anomalies is also followed commonly [11]. It is done because of the progression and understanding of stem cells, stem cell based cell therapy/treatment, organs, engineered organs [organs-on-chip, bioink (material that simulate the extracellular material physical properties of bioink such as tissue stiffness, cross-linking mechanism, viscosity, mass transfer properties, e.g., permeability and diffusion)-based organogenesis], growth factors or promoters, biomaterials, 3D/4D scaffold or bioprinting, devices, prosthetics, bioreactor scale organogenesis, and grafting (allo, auto, xenogenic), which singly or collectively have

simulated tissue engineering products and devices to work as pragmatism [9,11–14]. However, despite the tremendous advancement in different fields of the TE and RE, there is a risk that technical developments will outstrip the capacity of existing regulatory frameworks to cope with these novel products (Fig. 12.1). The comprehensive understanding of this chapter would cover basic background of the bionanomaterials, underlying physiochemical understanding, multidimensional printing (2D, 3D, and scaffold), and recent frame shift progression in terms of translational application considering social and ethical policies.

2. History and present status

2.1 History

History of the use of nanoparticles traces way back to the fourth-century AD by the Roman. However, the introduction of nanotechnology to medicine and the pharmaceutical field started long back in the 1990s. Furthermore, nanobiotechnology ushered in biological avenues such as biochemistry, molecular medicine, genetics, microbiology, and therapeutics with the invention of high-resolution microscopy. The fundamental scientific concept of nanoscience and nanotechnology was first perceived from a talk by physicist R Feynman at an American Physical Society (APS) meeting on December 29, 1959; for this reason, he is regarded as the father of nanotechnology.

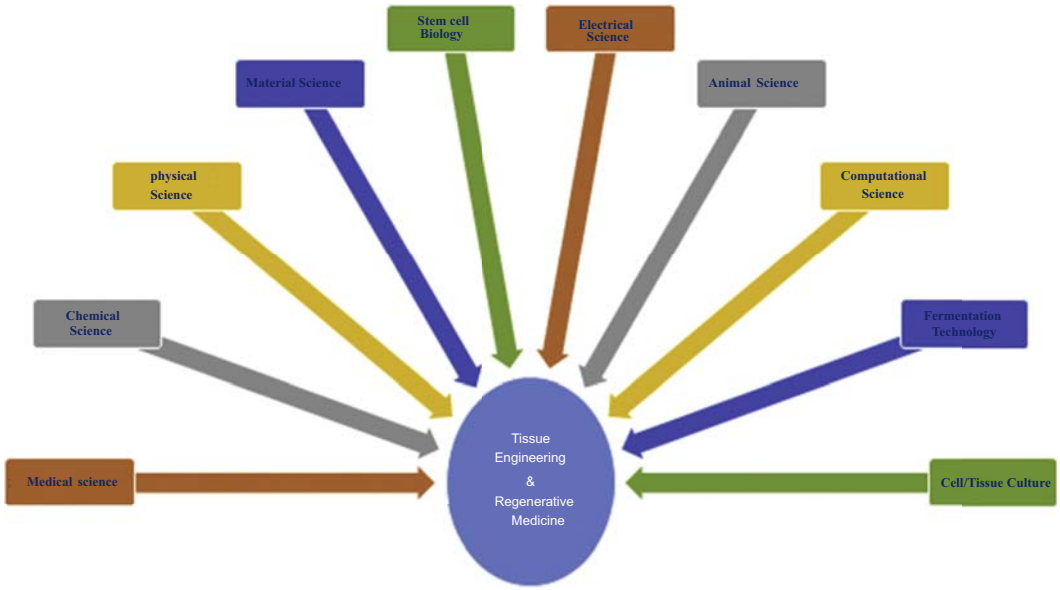

Figure 12.1
Different components of tissue engineering and regenerative medicine.

Professor Feynman proposed, "Why can't we write the entire 24 volumes of the Encyclopedia Britannica on the head of a pin?" [15]. Nevertheless, the concept remained in the doldrums until the discovery of a scanning tunneling microscope (STM) by physicists G Binnig and H Rohrer in 1981 [16], then onward people realized the importance of nanotechnology. On the scale, dimension corresponds to the 1000 millionths of a meter (10^{-9} m), whereas the term nanoscience is the study of the structure of material at the nanoscale, and nanotechnology explores the technology of nanoscience in multiple applications of practical applicability [17]. Currently not a single discipline is untouched by the application of nanotechnology, which includes physics, material science, chemistry, computer science, engineering, and biomedical sciences.

Parallel to the discovery of innovative microscopes, biological revolutionized discoveries were also made, such as the structure of the cell and its organelles, cellular and molecular communications, the mechanistic role of macro- and micromolecules in cell−cell interaction, and functionality of organ or tissue system. More to appreciate, the discovery of DNA and RNA during 1950s and 1960s notably renovated the approach of genetics toward translational value for the patient care or medical ailments [18]. The past two decades have considerably witnessed a significant revolution in the nanotechnology application for human health ranging from tissue engineering to the targeted drug or molecule delivery. The current scientific confrontations such as controlled design of the organ or tissue, biocompatible production, and desired transplantation have drawn the scientific fraternity interest to address the unresolved predicament and imparted the scientific challenges in to breaking medical discoveries significantly. While Feynman's theory largely relied upon the "top-down" approach, the subsequent thoughts and innovations led to the "bottom-up" approach, the controlled and manipulated construction of nanostructures from the individual atoms, as described by K Eric Drexler et al. [19]. The theory was further implied to medicine, and the term "nanomedicine" was used in the literature published by Robert A Freitas [20]. In the 20th century, discovery of the "Magic Bullets" by Paul Ehrlich targeted drug delivery and marked the beginning of chemotherapy era [21]. The follow-up investigations on physicochemical functionalization of surface structure led to the production of monoclonal antibodies by GJ Franz Köhler and C Milstein in the 1970s [22]. The intensive research on "bionanoparticle as a carrier agent" added to the tissue specific delivery of biomolecules, and this idea was applied to the cancer treatment by Yasuhiro Matsumura and Hiroshi Maeda in 1986 [23]. The approach of targeted delivery combated the issue of systemic toxicity and serious adverse events (SAEs) to a greater extent in the treatment of many diseases. Thereby field of medicine has benefited a lot from nanochemistry and ongoing efforts are poised to unfold revolutionary changes in the nanomedicine [24].

2.2 Present status

Nanostructured manipulations add to the outstanding physiochemical properties to composite bionanostructures, which promote tissue regeneration and translate it to other biomedical applications. The modern technology has immensely added to the nanostructured system and thereby exponentially enhanced the surface contact area of the synthesized biomaterials. This approach has been extensively explored by scientists and industrialists to translate nanotechnology into biological carriers and skin regeneration methods [25]. The past two decades have observed substantial advances in the physicochemical virtues of nanomaterials, which could not have been possible without the expanding knowledge of dimensions, shapes, and composition of the nanomaterials. Stem cells are a key source as seeding cells, which can be used in the tissue engineering, repairing, and regenerative medicine [26]. The introduction of bionanomaterials, along with stem cells, has considerably potentiated the cell proliferation in the case of many neuronal and cellular manifestations [27]. The extracellular matrix (ECM) facilitates the conformation of tissue to enable it to perform its function. Bionanomaterials have been used to create ECM-mimic scaffolds for the tissue to attain their 3D structural conformations, facilitating their functional properties [28–30]. These synthetic scaffolds are of utmost useful in organ transplantation in cases of tissue injury, organ failure, or traumatic conditions. Researchers have confirmed the synergistic outcome of the combination of bionanomaterials with the natural scaffolds, where they not only improve the differentiation, but also ameliorate the functional competency based on these bionanomaterials [31,32]. The parallel advancement in imaging technology, attributed by nanotechnology, has boosted the validation of quality control of the designed biomaterial scaffolds prior to their practical implications [33]. With dramatic increase of the use of bionanomaterials in biological systems, there is a concomitant possibility of bionanotoxicity posing threats of systemic toxicity in regenerative medications. In view of the translational approach, principles for the targeting of endogenous stem cells as well as growth factors for the modulation of stem cells are of immense importance [34].

There are a variety of bionanocomposites used in the tissue regeneration process. Of which, the polysaccharides, collagen, and chitosan rank on the top, especially in stem cell tissue engineering [35]. Another critical application of the regenerative medicine is in the healing of burn injuries, wherein antibiotics fail because of the development of drug resistance in bacteria [36]. These bionanomaterials sensitize thermal bacteria to respond against antibacterial treatments, enabling cell proliferation and tissue regeneration. In most of the cases of cancer therapy, there is a fair chance of drug resistance and relapse, caused by the cancer stem cells. Scientists have taken advantage of these nanomaterials loaded

with drugs and a peptide or antibody specific to those stem cell markers [37,38]. These approaches have shown encouraging results in the targeted drug delivery with the advantage of specificity and pharmacological efficiency. Recently, a study proposed the use of a combination of graphene nanosheets and liposome as photoinducible drug delivery vehicles intending to augment the pharmacological accuracy [39].

The integration of nanomaterials to biological molecules has synergistically shown the proliferative and regenerative capacity. The biocompatible and nontoxic nanocomposites have been in use for tissue regeneration. The advancement of synthetic chemistry and its application for biological system have made nanocomposites as a promoter with high precision and efficient control.

3. Multidimensional bioprinting of tissues and organs

Multidimensional tissue, organ, and organ system have been well developed [40]. Later, the idea of including cells into multidimensional printed constructs developed, leading to the progress of 3D bioprinting [41,42]. Most common forms of the 3D cell culture systems are the prefabricated scaffold and hydrogel. In a nutshell, the 3D or 4D systems are considered as a practical alternative to in vivo organization [43,44].

Several multidimensional printing products have been accepted and approved by the US Food and Drug Administration (US FDA) such as implants, medical instructions, orthopedic devices, and restorative equipment suited to individual needs [45]. To date, though there are most multidimensional printing techniques, medical uses have included rigid, nonliving constructions designed to act as structural or space filling prostheses [46]. Such latest advances in the design and manufacture of nonliving implantable multidimensional printed structures demonstrate the promise of multidimensional printing technologies for producing innovative patient-specific products.

Advancement in microfluidics and tissue engineering collectively has generated one more advanced dimension in regenerative medicine, i.e., the fourth dimension of the cell and tissue culture. In three-dimensional organogenesis, some of the restrictions such as fabrication of hollow structure to develop vascular construct with multiscale vasculatures and to provide the adequate microenvironment for growth, proliferation, and differentiation of cells into thick 3D structure persist. The 4D bioprinting has a large potential to impact tissue engineering and regenerative medicine research toward more personalized and precise approaches that can be easily translated into the clinic [47,48].

Multidimensional bioprinting of the cellular components has faced several challenges [49]. Their challenge includes, but not limited to, switching from artificial materials (metals, ceramics, and plastics) to biological functional materials, preserving the micro- and macroscale regulation of mechanical properties, to achieve tissue designs with

functional heterogeneity, to develop the procedures for developing and expanding functional cells from the stem cells, and to interface the biopressed tissue with physiology [50].

3.1 Bioprinting techniques

The most exciting bioprinting technology implements the self-montage and auto order capability of cells, which can be congregated into three main classes based on the principles: (1) extrusion, (2) droplet, and (3) laser-assisted bioprinting [42,51–53]. Every bioprinting method has unique properties and has certain benefits and drawbacks in terms of printing capability, resolution, speed of deposition, bioink material and compatibility, ease of use, print speed, price and commercial availability, and basic biocompatibility.

Extrusion-based bioprinting uses the mechanical or pneumatic potential energy to extrude the bioink and resolve the creation of droplets induced by surface tension to draw the bioink in the shape of cylindrical filaments [53], whereas laser-based bioprinting uses laser technology to print the cells efficiently and precisely on a substrate [52]. This can be classified into two main categories: (1) photopolymerization processes and (2) cell transmission-based processes. Finally, droplet-based bioprinting uses acoustic, thermal, or electrical energy to print the cells encapsulated in small bioink droplets that are deposited and assembled layer by layer [54]. Droplet-based bioprinting can be classified into four methods, such as (1) inkjet bioprinting, (2) electrohydrodynamic jetting, (3) bioprinting with microvalves, and (4) acoustic droplet ejection (Fig. 12.2).

3.2 Applications of multidimensional bioprinted tissues and organs

Engineered tissue/organ counterparts have arisen as exciting multidivisional, in vitro models that can easily recapitulate the pathophysiology of specific goals [55]. The existing techniques in tissue engineering typically incorporate scaffolds and cells to build new viable tissues for medical applications. Despite major advances in synthetic tissue design, the failure of such conventional approaches to building structures with specific architectural topographies and the spatial positioning of cells have driven the quest for new substitutes [56]. Multidimensional bioprinting is a useful approach for development of multidimensional tissue/organ analogs.

Multidimensional printing enables a groundbreaking period in the design and production of medical devices. It is commonly utilized through layer-by-layer deposition to produce multidimensional scaffolds [57]. Biomaterials are typically distributed to different space points using a dispensing device to create a scaffold with well-controlled configuration. Three-dimensional bioprinting has been widely used for the production of tissue-engineered constructions because of its property of repeatability and high precision at

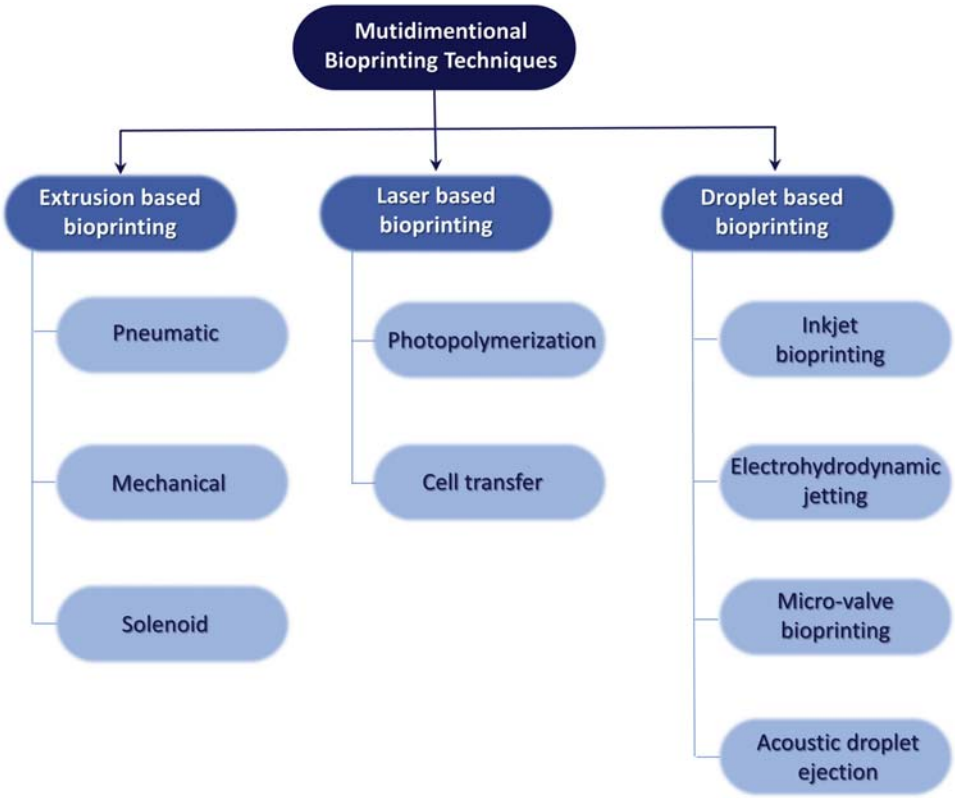

Figure 12.2
Bioprinting techniques and their classification.

manufacturing resolution. Methods including fused deposition modeling, precision extrusion deposition, targeted laser sintering, 3D printing, and stereolithography are used to substitute products treated with biocompatible materials such as natural and synthetic polymers, organic and inorganic ceramic materials, or recently developed biodegradable metals [52,53]. The application of multidimensional printing into tissue engineering offers the advanced proficiencies for rapid manufacturing of controlled tissue scaffolds having porosity and internal morphology and tunable mechanical and structural topographies. To direct the cellular environment, the customized multifunctional physiognomies have been improved by charging the selective drug or protein molecule [58].

In terms of its significant advantages for biological development of tissue scaffolds, the multidisciplinary printing is subjected to various restrictions especially when difficult transplant or application of tissue or organ is needed [57,59]. Cell positioning requires accuracy due to manually guided seeding and the position of cells on the microarchitecture of scaffolds. For the arrangement of seeding of cells, cell positioning is quite hard to align

during the scaffold build. However, in a normal tissue and organ system, many cell types/classes are arranged and communicate to each other in a complicated manner. Furthermore, large-density seed cells are very problematic because cells can only bind themselves to the surface of the scaffold and cannot infiltrate biomaterial inside the scaffold. Biomaterials from scaffolds often occupy a large amount of space that does not enable cells to expand into sufficient numbers [57]. In fact, the requirement for a vascular network is important to the production of thick tissue and organ, to allow an effective exchange of the media to sustain the cells in an oxygenated, stable, and functionally viable manner [60]. Such challenges have driven researchers to establish bioprinting techniques in which cells are enclosed in large cell densities and printed and patterned appropriately to produce anatomically accurate tissue buildings that associate patterned cells as in natural tissues and organs [50].

4. Bioprinting and biomodeling of physical and chemical foundation

In tissue engineering, to generate functional tissue construct, it is necessary to have prompt biochemical and biophysical intersections. The possible advancements in the field can be valued by 3D bioprinting, which is made feasible by printing technology, cell biology, and materials science. While fabricating 3D bioprinting, accurate positioning of biochemical, biophysical, and biological materials and living cells is required to generate 3D structures [46]. A wide variety of physical parameters are considered to optimize the 3D bioprinting (Table 12.1). First bioprinter was developed by Charles Hull in 1984 [47]; bioinks are materials used to produce engineered/artificial live tissue using 3D printing.

Table 12.1: Physical and chemical intersections, impact and preventions in tissue engineering and regenerative medicine.

Physical and chemical parameter	Impact	Prevention
Shear stress	Can cause mechanical damage to the cell membrane resulting in significant loss in the cell viability	Shear thinning (i.e., decrease in viscosity due to an increase in pressure)
Stiffness	Affect the viability, phenotype, and contractile properties	Can be minimized by applying appropriate value of pressure
Biophysical cues	Determine several interstitial structures and functions	Not to be overlooked when designing the and testing in tissue engineering
Photoinduced cross-linking	Produce potentially toxic photoinitiators	Can be minimized by using chemical cross-linking methods
pH	Effect differentiation, proliferation, and migration of cells in tissue	Can be minimized by using optimal pH conditions

The materials used for bioink (alginate, agarose, gellan gum, hydrogel etc.) mimic the extracellular material (ECM)) physical properties, such as viscosity, cross-linking mechanism, tissue stiffness, mass transfer properties (e.g., diffusion and permeability), and biodegradability [61,62].

4.1 Physical intersections

4.1.1 Shear stress

Shear stress plays an important role and is unavoidable during the dispensing process. A higher shear stress can cause mechanical impairment to the cell membrane, resulting in substantial loss in cell viability. Numerous parameters affect the level of sheer effect like viscosity, nozzle size and design, temperature, and pressure. These parameters deregulate the various cell signaling and protein expression patterns [63]. During the biofabrication, high viscosity increases the cell fidelity, while lower viscosity helps in mimicking the microenvironment of the embedded cells in tissue engineering.

4.1.2 Physical cross-linking

To build the 3D construct, tissue requires fast and uniform cross-linking. The most predominant methods of cross-linking are physical, chemical, and photocross-linking, usually using ultraviolet (UV) or visible light [64]. In light-based cross-linking, the controlled intensity of light allows added cross-linking homogeneously. The physical nature of the cross-linking also depends on the wide variety of photocross-linker reagents. Concentration of the reagent in the hydrogel alters the degree of cross-linking and controls the physicochemical properties of the construct (e.g., stiffness, degradation rate, and permeability) [65,66].

4.1.3 Stiffness

While constructing the 3D engineered tissues, stiffness plays an imperative role in cell viability, development, and function, especially in cardiac tissue maturation in vitro. Stiffness can directly affect the viability, phenotype, and contractile characteristics of the cardiac muscles [67]. The stiffness value of 1−18 kPa is similar to the stiffness value of native myocardium and has been revealed to support the cardiac myocyte functionality, including sarcomere alignment, force generation, and contractile rhythm [68]. Considering all these parameters stiffness plays an important role in cardiac tissue printing.

4.1.4 Biophysical cues

The ECM in a tissue is composed of diversified biomolecules such as glycosaminoglycans (GAGs), proteins, and polysaccharides, which are organized from the nanometer scale to micrometer, fibrils, and fibers. Morphological parameters including shape, size, elasticity, and highly ordered meshwork regulate the behavior in different cell types. In tissue

engineering, biophysical cues determine the several interstitial structures and functions. In cartilage tissue, it helps in joining of the bones and joints, variations in chondrocyte occupation, calcification, and collagen network density helps in producing a durable ECM, which can bear considerable shear stress [69,70].

Biophysical cues are important in determining the significant architectural differences in the tissues. Biochemical collagen is most abundant protein in the human body and considered as the primary component of corneal or cartilage tissue ECMs. However, differences in the biophysical cues at the nanometer and micrometer scale provide structural differences to both the tissues having different tissue compliance, mechanical integrity, and basal membrane (BM) topography. Therefore, biophysical cues should not be overlooked when designing and testing in tissue engineering [71]. In designing a tissue through bioengineering aspects, biophysical structures are equally important as the biochemical composition of a tissue. Cells interact widely through the ECM when structuring tissue engineering scaffold importance of biophysical cues must be kept in mind.

4.2 Chemical intersections

4.2.1 Chemical cross-linking

Chemical cross-linking approach provides several competencies as compared with physical cross-linking methods. Photoinduced cross-linking via UV radiation in physical methods can expose the encapsulated cells to possibly toxic photoinitiators and deleterious UV radiations. However, on the other side, chemically made hydrogels are more biocompatible [72]. Numerous bioprinting compatible hydrogels rely on chemical cross-linking methods. One of these is alginate, which relies on calcium-mediated cross-linking immediately. Also, calcium divalent ions are found to be helpful in instantaneous chemical cross-linking between alginate gelatin-based hydrogel. It also helps in fabricating the layer-by-layer resolution, resulting in the fabrication of highly reproducible, complex architectures [65].

4.2.2 Chemical additives and pH

Physicochemical properties of the hydrogel depend on some key parameters including pH, composition, cytotoxicity, and osmolarity. Each of these properties is vital for the success of tissue bioprinting and its maturation in in vitro conditions [73]. It can be assumed by printing fidelity of collagen-based bioinks, which are highly pH dependent and maintain the best performance at a pH of 8.0–9.50 range. Some chemical additives such as Rho-kinase inhibitor (ROCK inhibitor; ROCKi) help in maintaining the cardiac cell homeostasis, which in turn helps in cell survival, differentiation, proliferation, and migration [74]. Another important example of chemical additives is the use of antibacterial nanoparticles (e.g., iron oxide nanoparticles), which can be used to prevent infection within engineered cells and tissues.

5. Regeneration of biomedical products

Worldwide efforts are being made for developing biomedical products to improve health care and medical research [75]. These products are utilized in the biomedical and pharmaceutical utility, such as prostheses and implants, implanted insulin pump, tissue engineering scaffolds, nanoantibiotics for infectious diseases, immunoassays, anticancer drugs, and biomolecular sensing using diagnostic sensors (lab-on-a-chip) [76]. Some of these products are already in the market, more will be there soon, and others still need to go miles before becoming a reality.

Quantum dot–based nanotechnology analytical tools are currently in practice [77]. One of such approaches is where the DNA in a sample is identified by using its bonding properties with molecules at a certain concentration, which are loaded in polymeric spheres having submicrometer size of quantum dot mixture. Each of these quantum dots offers a unique spectral color code [78]. This approach is extremely useful in studying larger sample sets with a plethora of single nucleotide polymorphisms (SNPs). Indeed, this approach is being used to analyze SNPs in the genes encoding for several enzymes of the cytochrome P-450 family [79]. Likewise, the antibodies wrapped over nanowires can also be used in the detection of viruses in biological fluids, for example, blood or serum, since the bonding of a single virus particle to the wrapped antibody leads to changes in electric conductance of the nanowire. This approach has been used in detecting the early stage infection in the human body [80].

Similarly, chip-based biosensors are also in the clinical practices. These chips can be used to analyze biopolymers and are capable of manipulate the cells. Furthermore, biochips can be used in the detection of the pathogens [81]. Lab-on-chip approach is being employed in detection of lead in blood. Moreover, photonic explorers for bioanalysis with biologically localized embeddings (PEBBLEs), a lineage of "lab-on-chip" approach are also being used in the measuring concentrations of small ions and molecules including magnesium, zinc, calcium, and hydrogen or glucose in the cellular pool [82,83].

Artificial joints, for example, hip, are sustained for use only for 10–15 years. Once, their usual life span is about to finish, complications start arising leading to life-threatening situations. With the aid of nanotechnology, such complications can be abstained. Wear- and tear-resistant implants are made up of alloys of cobalt or chromium or titanium in thin layers [84,85]. However, the functionality and safety of nanotechnology-coupled stents still need to be validated in the animal model or clinical trials. Other category of implants include insulin pumps, morphine pumps, membranes with nanopores in microchips for drug delivery, bladder stimulators (for controlled emptying of the urinary bladder), cochlear implants (for restoring hearing), pacemakers and defibrillators

(to regulate heart beat), deep brain stimulators (for patients with Parkinson's disease), and retinal implants (to restore the sight in patients with a damaged retina), which are under their developmental stage [85].

Despite holding an enormous potential, scientific progress in nanobiomedical products is still slow because of their long-term health, safety, social, environmental, and ethical concerns. Other major challenges associated with these products are their need for large-scale production, lack of a well-established nanoscale industry, high production costs, fund scarcity, and lack of clear safety and regulatory guidelines [86]. Enough data related to exposure, cellular toxicity, and pharmacokinetics studies of bionanomaterials are not available. The recent boom in the invention of bionanomaterial and biomedical products is that there is a strict need for their regular assessment, for example, unintentional or intentional environmental exposure for medical use. The consequences of nanoparticles at the cellular level, after entering the human body, are largely unknown. In this context, nanoparticle-derived biosensors used in bioanalytical or immunological assays, nanorobots in wound repairing, and destroying tumor tissues and viral vectors employed in gene therapy are of major concern. These particles are too small to be controlled at the cellular level and may deliver harmful and toxic substances, thereby affecting the overall health of an individual. Another challenge associated with bionanomaterial is the selection and optimization of materials used for biomedical technologies and environmental disposal of nanowaste. We are not aware of the presence of nanowaste in the environment as they do not exist naturally, and secondly their size is in the nanoscale range. The distribution and disposal of engineered nanoparticles and bionanomedical products should be appropriately controlled to avoid any health hazards.

6. Next-generation regenerative therapies

The translational research has improvised the healthcare structure. Outcome has generated the way to control the infectious disease, process of the healing, and availability of the spare body parts by organogenesis. It is very important to understand the affected body region and to assess the risk, which helps in regenerative medicine for the personalized treatment with stem cell or cellular therapies. Induced pluripotent stem (iPS) and embryonic stem (ES) cells are prominent regenerative cell resources, which show their potential for clinical practices [87,88]. The ES cells are generally derived from embryos and are pluripotent, whereas iPS cells are derived from somatic cells unveiled to an inducible pluripotent transcript. The iPS cells are generated from the patient's body cells and so have less rejection and therefore have least apprehension as far as concern with ethical clearances and implications [89–91]. Furthermore, direct reprogramming by retroviral injection has opened bright futuristic alternatives and is considered the best substitute to the bypass surgeries [92]. Further studies are targeted to control the cell

growth at targeted regions to avoid risk of tumor formation by ES or iPS cells. The regenerating cells are also getting tested for tissue variation formation at cardiomyocytes, hepatocytes, hematopoietic cells, pancreatic cells, vascular cells, and neural cells. Another application of regenerating cells in ex vivo is to engineer cellular grafts or to create a suitable microenvironment for cells reprogramming. In one of the cardiac maturation studies, tissue derived from iPS cells in hydrogels with aligned fibers showed increased gene expression in presence of electrical stimulation. Tissue regeneration has numerous potential applications in the field of cardiac disease, neuroregeneration, and neovascularization.

Currently, regenerative medicine is progressing through clinical stages of FDA approval and uses in critical therapies designed in pathologies such as graft fabrication, tissue repairing, and at place of scaffolding materials. Silva et al. [93] tested these adipose stem cell—derived vesicles in porcine for postoperative digestive fistula treatment with thermo actuated delivery and reported utmost success rate. A recent study by Zhu et al. [94] reported metabolic reprogramming iPSC-derived natural killer cells via deleting cytokine-inducible SH 2 (CISH) gene in human to improve in vivo persistence and enhanced antitumor activity. Behfar et al. [95] summarized the literature on stem cell—based trials for current promising regenerative therapies for the cardiac diseases. Globally, more than 7000 patients have been treated with autologous stem cell—based therapy, but still functional variability inherent to these cells remains the main factor in restraining presentation of cell-based therapies. Liu et al. [96] repaired bone in rabbit model and reported enhancement with bioenergetic active material (BAM) scaffold as compared with commercialized polylactic acid (PLA) and calcium phosphate ceramic scaffolds. An intramitochondrial metabolic bypass was established to internalize energy active units, which elevates mitochondrial membrane potential to improve the level of bioenergy to expedite the bone formation (Fig. 12.3). The bioenergetic active material can be precisely degraded and useful in bone repair application and thus possess advantages for the controlled degradation in fragments (B). The bone regeneration mechanism and significant improvement were observed with the BAM model as compared with PLA method (C, D). The rabbit femur was experimented to study the newly formed bone in BAM group, and a new connection was found at both the ends of bones, whereas PLA group did not show any bridging around the bone. Furthermore, micro-CT 3D reconstruction also confirmed the significantly repaired tissue at defected site in the BAM group compared with PLA scaffolds at week 12 (D). Regenerative medicine progress in cardiovascular field is important, and recent development with cardiac patches found many advantages in heart failure or myocardial infarction [97]. Dvir et al. [98] presented a method to engineer cardiac patch with mature vasculature by heterotopic transplantation onto the omentum. Vascularized cardiac patch for 7 days on the omentum was transplanted to the myocardial infarcted rat hearts. After 4 weeks of the implantation, structural and electrical integration

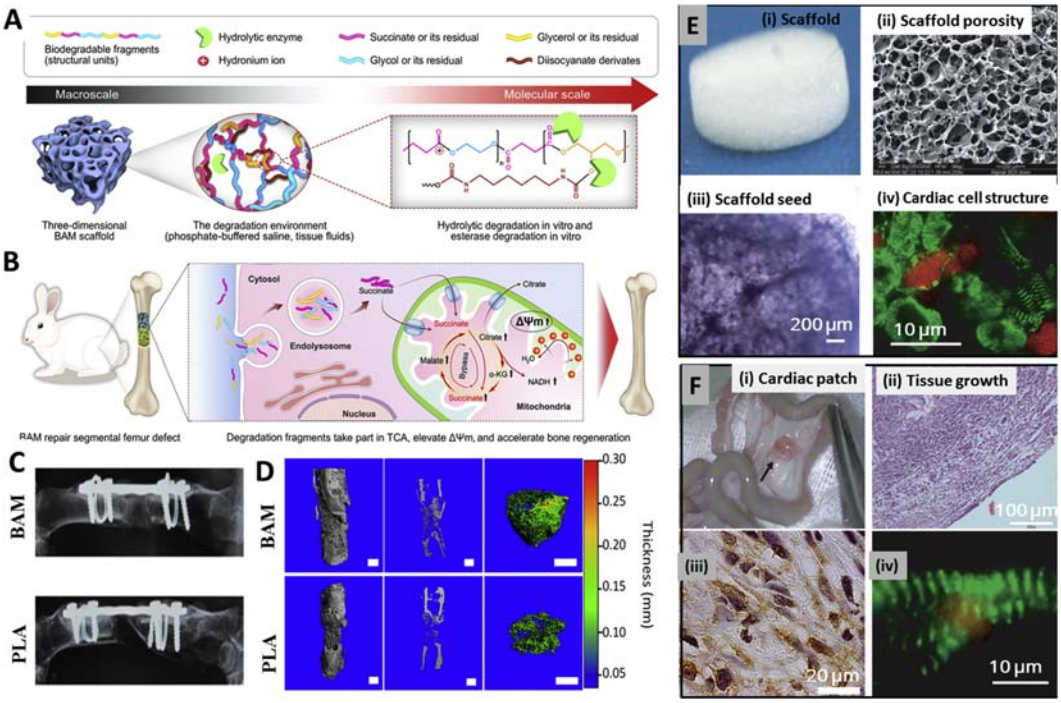

Figure 12.3

Schematic of BAM scaffold degradation on tissue regeneration and enhancement of bone regeneration in vivo.

(A) Illustration of the chemical structures and designed in vitro/in vivo degradation mechanism of BAMs. (B) Bone regeneration mechanism. (C) Rabbit femur at the fourth week indicating regenerated new bone in BAM group and no bridging for the PLA group. (D) Micro-CT at 12 weeks demonstrating the repair tissues at the defect sites with BAM and PLA scaffolds (scale bars = 2 mm). Development of a cardiac patch in alginate sulfate/alginate scaffold before cell seeding: [E (i)] macroscopic view, (ii) porosity with scanning electron microscopy, (iii) cardiac patch (with 2.5 × 106 cardiac cells), (iv) structure of cardiac cell in scaffold (antiactin immunostaining green, nucleus red). [F (i)] Vascularization of cardiac patch at the seventh day of the omentum transplanted and patches stitch to the omentum. [F (ii)] H&E-stained cross section confirms tissue growth into the scaffold. Lower right is the patch edge. [F (iii)] Anti-Tn-T immunostaining of the thin section in the omentum-generated cardiac patch (brown). [F (iv)] Cardiac cell striation confirmation (antiactin immunostaining green) with confocal microscopy *(AD) Reproduced with permission from H. Liu, Y. Du, J.P. St-Pierre, et al., Bioenergetic-active materials enhance tissue regeneration by modulating cellular metabolic state, Sci. Adv. 6 (13) (2020) eaay7608. https://doi.org/10.1126/sciadv.aay7608 and (E—F) Reproduced with written permission from T. Dvir, A. Kedem, E. Ruvinov, et al., Prevascularization of cardiac patch on the omentum improves its therapeutic outcome, Proc. Natl. Acad. Sci. U. S. A. 106 (35) (2009) 14990—14995. https://doi.org/10.1073/pnas.0812242106.*

of the vascularized cardiac patch was observed in host myocardium. This study promises that the grafting prevascularized cardiac patch on the omentum could improve cardiac function.

Polymeric scaffold has advantages over others in rapid formation of a mature vasculature. Richardson et al. [99] proposed a polymeric approach for tissue-specific delivery of dual growth factors with a controlled dose and rate of delivery. Scales et al. [100] reviewed interactions between microbiome in wound repair and development of fibrotic lesions. It is now understood that culture independent microbiology was utilized in bacterial communities in the wounds, but surrounding mucosa still under scanner to understand the cause and effect of relationships between microbiome and wound repair mechanisms. Mesenchymal stem cells (MSCs) could also provide therapeutic implications because they trigger antiapoptotic events and hence avoid the degeneration of diseased organ [101]. An augmented paracrine gradient is witnessed in the perimeter of the diseased area, which directs in an increment of tissue-specific MSCs at region of injury or infection to promote healing. The paracrine signaling mechanism could provide applications in regenerative field for bone regeneration, myocardial infarction, and wound healing.

Tissue reinnervation has many challenges in disease, trauma, or transplantation. The regenerative medicine field needs control over the growth of stem cells for effective posttransplantation and needs technology advancement in developing fully vascularized grafts, which could increase survival efficacy. However, more work needs to be done on creating an environment in host patient body to grow required cells for replacement. Three-dimensional cell cultures could allow testing the regenerative medicine in various environments and impact with several factors, which could help with translation of regenerative medicine in clinical applications [3,102].

7. Application and challenge: an evolving paradigm

The TE and RM are quite interchangeable term, and moreover, tissue engineering word was termed well before the regenerative medicine. Selective matrix is used with respect to the cell in use, and thereby the formation of tissue is achieved [103]. However, the potential of stem cell is exploited by various strategies underlying in the tissue engineering, which consequently give rise to the basis for regenerative medicine [104]. The hidden potential of stem cell easily mimics the functionality of targeted organ, which is required to formulate. The evolving paradigm shift solemnly depends on the change in multidisciplinary sciences, such as material sciences, biomechanics, cell biology, and medical sciences as it is well integrated, and their integrations results in a wide variety of translational applications of tissue engineering in regenerative medicine. Presently, there are various tissue engineering products, which are being used for patient care, diagnosis, and research (Table 12.2). Skin grafts, cartilage, supplemental bladders, small arteries, and

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].

S. No.	Location	Company	Specific field
		Australia	
1	Armadale, VIC	Cynata Therapeutics	Stem cell manufacturing technology
2	East Melbourne	Cell Therapies	Cellular therapies
3	Melbourne VIC	Living Cell Technologies	Regenerative medicine
4	Melbourne VIC	Mesoblast	Regenerative medicine
6	Pymble NSW	Regeneus	Stem cell therapy
7	South Melbourne VIC	Ascend Biopharmaceuticals	Immunotherapy
		USA	
8	Alameda, CA	Orthocyte (BioTime)	Cellular therapies
9	Beverly Hills, CA	Capricor Therapeutics	Stem cell heart treatments
10	Beverly Hills, CA	Neurogeneration	Autologous therapy
11	Carlsbad, CA	International Stem Cell	Proprietary stem cell induction
12	Carlsbad, CA	Targazyme	Cell therapy
13	Culver City, CA	NantCell	Cellular therapy
14	Emeryville, CA	Adheren	Cancer immunotherapy
15	Fremont, CA	Asterias Biotherapeutics (BioTime)	Embryonic stem cell product
16	Irvine, CA	Caladrius Biosciences	Stem cell research products
17	Irvine, CA	Invitrx Therapeutics	Autologous stem cell therapy, therapeutic and cosmetics
18	La Jolla, CA	Ankasa Regenerative Therapeutics	Proprietary formulations of WNT stem cell activators
19	La Jolla, CA	StemGenex	Stem cell therapy
20	La Mesa, CA	Regen BioPharma	Regenerative medicine, cell therapy, small molecule
21	Los Angeles, CA	Iovance Biotherapeutics	Adoptive cell therapy
22	Menlo Park, CA	Adicet Bio	Immunotherapies
23	Menlo Park, CA	Adverum Biotechnologies	Adenoassociated virus delivery, gene therapy
24	Mission Viejo, CA	Generatx	Stem cell therapy
25	Mountain View, CA	Apceth	Cell therapies
26	Mountain View, CA	Human Longevity Inc	Genotype/phenotype database for therapeutic/diagnostics discovery
27	Mountain View, CA	PCT Cell Therapy (Caladrius Biosciences)	Cell therapy development support
28	Mountain View, CA	SanBio Co Ltd	Cellular therapies
29	Novato, CA	Cellular Dynamics (Fujifilm)	Induced pluripotent stem cells
30	Palm Desert, CA	Cell Surgical Network	Stem cell isolation/treatments
31	Palo Alto, CA	Cellular Biomedicine Group	Cell therapy
32	Poway, CA	VetStem Biopharma	Stem cell therapy for animals
33	Redwood City, CA	Bullet Biotechnology	Immunotherapy

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
34	Redwood City, CA	OncoMed Pharmaceuticals	Cancer stem cells
35	San Carlos, CA	BioCardia	Personalized marrow derived cell therapy
36	San Diego, CA	Animal Cell Therapies	Veterinary stem cell therapies
37	San Diego, CA	CardioCell (Stemedica)	Cell therapy
38	San Diego, CA	Cytori Therapeutics	Cryopreservation systems, cellular therapy
39	San Diego, CA	F1 Oncology	CAR-T
40	San Diego, CA	Histogen	Regenerative medicine
41	San Diego, CA	Human Longevity Inc	Genotype/phenotype database for therapeutic/diagnostics discovery
42	San Diego, CA	Neurogeneration	Autologous therapy
43	San Diego, CA	Stemedica Cell Technologies	Stem cell production
44	San Diego, CA	ViaCyte	Stem cell therapies
45	San Diego, CA	Vital Therapies	Extracorporeal cellular therapy for liver disease
46	San Diego, CA	Xcelthera	Stem cell therapy
47	San Francisco, CA	Tempo Bioscience	Biosensor assays, stem cells, services
48	San Mateo, CA	Medeor Therapeutics	Cellular immunotherapy
49	South SF, CA	Chimera Bioengineering	CAR-T therapies
50	South SF, CA	Neurona Therapeutics	Neuronal stem cell therapies
51	South SF, CA	VistaGen Therapeutics	Stem cell technology
52	Yorba Linda, CA	DaVinci Biosciences	Cellular therapies
53	Aurora, CO	MBC Pharma	Bone seeking treatments
54	Aurora, CO	Taiga Biotechnologies	Small molecules, cell therapies
55	Aurora, CO	Taiga Biotechnologies	Small molecules, cell therapies
56	Alachua, FL	AxoGen	Nerve tissue processing
57	Jupiter, FL	BioRestorative Therapies	Autologous stem cell therapy
58	Orlando, FL	Immune Therapeutics	Immunotherapy
59	Sunrise, FL	U.S. Stem Cell	Cell therapies and delivery
60	Tampa, FL	Morphogenesis	Cells as diagnostics
61	Tampa, FL	Saneron CCEL Therapeutics (Cryo-Cell International, Inc)	Cellular therapy
62	West Palm Beach, FL	F1 Oncology	CAR-T
63	Athens, GA	ViaCyte	Stem cell therapies
64	Atlanta, GA	Metaclipse Therapeutics	Personalized cancer therapy
65	Atlanta, GA	Spher Ingenics	Cellular therapies
66	Honolulu, HI	Tissue Genesis	Adipose cell isolation
67	Ames, IA	NewLink Genetics	Cell therapy, small molecules
68	Indianapolis, IN	Cook General BioTechnology (Cook)	Tissue processing, cellular therapy and contract research
69	Baton Rouge, LA	NuPotential	Cell line production

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
70	Boston, MA	Anagenesis Biotechnologies	Cell therapy, small molecules
71	Boston, MA	Asymmetrex	Adult stem cell "production"
72	Boston, MA	Celyad	Stem cell differentiation
73	Boston, MA	Inform Genomics	Genomic-based medicines
74	Boston, MA	ORIG3N	iPS cell therapy
75	Boston, MA	Vor BioPharma	CAR-T stem cell therapy
76	Boston, MA	Ziopharm Oncology	Cellular therapies
77	Cambridge, MA	AVROBIO	Cellular and gene therapies
78	Cambridge, MA	eGenesis	CRISPR for xenotransplantation
79	Cambridge, MA	Magenta Therapeutics	Stem cell, bone marrow transplant technology
80	Cambridge, MA	MirImmune (Rxi Pharma)	Cancer immunotherapy
81	Cambridge, MA	Neon Therapeutics	Vaccines and T cell therapies
82	Cambridge, MA	OvaScience	Fertility, mitochondria transplantation
83	Cambridge, MA	Pathfinder Cell Therapy	Cell-based therapy
84	Cambridge, MA	Rubius Therapeutics	Enucleated cell therapeutics
85	Cambridge, MA	Semma Therapeutics	Diabetes stem cell treatments
86	Cambridge, MA	TCR2 Therapeutics	T cell immunotherapy
87	Cambridge, MA	Unum Therapeutics	Cellular immunotherapies
88	Cambridge, MA	Vericel	Cellular therapy
89	Natick, MA	Regeno CELL Therapeutics	Stem cell therapy
90	Waltham, MA	Juno Therapeutics	Immunotherapy, CAR-T
91	Waltham, MA	Neovii Biotech	Stem cell therapy, biologics
92	Waltham, MA	ViaCord (PerkinElmer)	Cord blood banking
93	Bethesda, MD	AnGes	Gene therapy
94	Clarksville, MD	Neuronascent	Small molecules, stem cells
95	Columbia, MD	Osiris Therapeutics	Cellular matrix treatments
96	Gaithersburg, MD	NexImmune	Artificially engineered antigen presenting cells
97	Gaithersburg, MD	Trevigen	Cell assays
98	Germantown, MD	Neuralstem	Stem cell technology
99	Germantown, MD	Orgenesis	Autologous cellular conversion
100	Rockville, MD	TissueGene	Regenerative therapies for orthopedic disorders
101	Ann Arbor, MI	Vericel	Cellular products
102	Research Triangle Park, NC	ZenBio	Human cells, media, kits, tissues
103	Winston–Salem, NC	Cellf BIO	Regenerative medicine–based therapy for fecal incontinence
104	Winston–Salem, NC	Plureon	Pluripotent stem cells derived from amniotic fluid and placenta

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
105	Lebanon, NH	Celdara Medical	Cellular therapy, diagnostics
106	Allendale, NJ	PCT Cell Therapy (Caladrius Biosciences)	Cell therapy development support
107	Basking Ridge, NJ	Caladrius Biosciences	Adult stem cell storage
108	Eatontown, NJ	Personal Cell Sciences	Autologous stem cell firming serum for esthetics
109	Hackensack, NJ	BrainStorm Cell Therapeutics	Autologous, adult stem cell therapy technology
110	Little falls, NJ	Regenicin	Autologous skin cell therapy
111	New Brunswick, NJ	Celvive	Cell therapy
112	New Brunswick, NJ	Chromo Cell	Cell therapy
113	North brunswick	Chromo Cell	Drug discovery, cellular therapy
114	New York, NY	BlueRock Therapeutics	Stem cell therapies
115	New York, NY	Caladrius Biosciences	Adult stem cell storage
116	New York, NY	DanDrit Biotechnology	Cancer vaccines
117	New York, NY	Dompé	Biologics, small molecules, OTC
118	New York, NY	Helocyte (Fortress Biotech)	Cytomegalovirus, oncology immunotherapies
119	New York, NY	Mesoblast	Regenerative medicine
120	New York, NY	Stemline Therapeutics	Cancer stem cells
121	Exton, PA	Fibrocell Science	Personalized skin therapy
122	Philadelphia, PA	Adaptimmune Therapeutics	T cell cancer therapy
123	Pittsburgh, PA	Celsense	Real time MRI detection of inflammation and cellular therapeutics
124	Providence, RI	Semma Therapeutics	Diabetes stem cell treatments
125	Austin, TX	TeVideo Biodevices	Cell therapy for breast reconstruction
126	Floresville, TX	Targazyme	Cell therapy
127	Houston, TX	Bellicum Pharmaceuticals	Cellular therapy
128	Houston, TX	Inform Genomics	Genome-based medicines
129	Houston, TX	In Generon	Stem cell collection and processing technology
130	San Antonio, TX	Cytori Therapeutics	Cryopreservation systems, cellular therapy
131	San Antonio, TX	StemBioSys	Stem cells
132	The Woodlands, TX	Opexa Therapeutics	Cell therapy
133	Salt Lake City, UT	Disc Genics	Spinal stem cell therapies
134	Redmond, WA	Astarte Biologics	Cell products
135	Seattle, WA	AVM Biotechnology	Stem cell technologies
136	Seattle, WA	Immusoft	Autologous B cell conditioning

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
137	Seattle, WA	Juno Therapeutics	Immunotherapy, CAR-T
138	Seattle, WA	Nohla Therapeutics	Universal donor cell therapy
139	Seattle, WA	Universal Cells	Nonimmunogenic cells
140	Madison, WI	Cell Line Genetics	Pharmaceutical services
141	Madison, WI	Cellular Dynamics (Fujifilm)	Induced pluripotent stem cells
142	Madison, WI	Stratatech (Mallinckrodt)	Cell therapy, tissue engineering
		Canada	
143	Vancouver, BC	Repli Cel Life Sciences	Autologous cell therapies for healing
144	Toronto, ON	AVROBIO	Cellular and gene therapies
145	Toronto, ON	ExCell Thera	Growing blood stem cells for therapeutic use
146	Toronto, ON	Trillium Therapeutics	Stem cell therapy
147	Vancouver	Stem cell Technologies	iPSCs research products
		European Union	
148	Gosselies, Belgium	Bone Therapeutics	Cell Therapy
149	Mont-Saint-Guibert, Belgium	Celyad	Stem cell differentiation
150	Mont-Saint-Guibert, Belgium	Promethera Biosciences	Liver disease treatments
151	Copenhagen, Denmark	DanDrit Biotechnology	Cancer vaccines
152	Corbeil-Essonnes, France	I-stem	Human pluripotent stem cells, of embryonic origin or iPSCs
153	Fontenay-aux-Roses, France	Brainvectis	Viral vector Therapy
154	Illkirch Graffenstaden, France	Anagenesis Biotechnologies	Cell therapy, small molecules
155	Mulhouse, France	Cell Prothera	Stem cell transplant for cardiac conditions
156	Mulhouse, France	Cell Prothera	Stem cell transplant for cardiac conditions
157	Toulouse, France	InvivoGen Therapeutics	Gene and immunotherapies
158	Valbonne, France	TxCell	Personalized cellular immunotherapies
159	Cologne, Germany	Axiogenesis	Stem cell products
160	Graefelfing, Germany	Neovii Biotech	Stem cell therapy, biologics
161	Munich, Germany	Apceth	Cell therapies
162	Ottobrunn, Germany	Apceth	Cell therapies
163	Tuebingen, Germany	Immatics Biotechnologies	Cancer immunotherapy
164	L'Aquila, Italy	Dompé	Biologics, small molecules, OTC

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
165	Milan, Italy	Molecular Medicine	Biologics, small molecules, cellular therapy
166	Milano, Italy	Dompé	Biologics, small molecules, OTC
167	Napoli, Italy	Dompé	Biologics, small molecules, OTC
168	Rome, Italy	Okairos	T cell–based vaccines
169	Vecchiano, Italy	Galileo Research	Cell therapy, contract research
170	Amsterdam, Netherlands	Kiadis Pharma	Stem cell treatment
171	Maastricht, Netherlands	CiMaas	Cellular immunotherapy
172	Maastricht, Netherlands	Pharma Cell	Contract cellular manufacturing
173	Lodz, Poland	Celther Polska	Stem cell lines
174	Viken, Sweden	Tikomed	Regenerative medicine
175	Basel, Switzerland	Targazyme	Cell therapy
176	Rapperswil, Switzerland	Neovii Biotech	Stem cell therapy, biologics
177	Abingdon, UK	Adaptimmune Therapeutics	T cell cancer therapy
178	Bridgend, UK	ReNeuron	Stem cell therapies
179	Cambridge, UK	OxStem	Stem cell drugs
180	Cambridge, UK	Talisman Therapeutics	Alzheimer's stem cell model
181	Cardiff, UK	Celixir	Regenerative medicine
182	Croydon, UK	AnGes	Gene therapy
183	Deeside, UK	Cytori Therapeutics	Cryopreservation systems, cellular therapy
184	Edinburgh, UK	Roslin Cells	Stem cells
185	London, UK	Cell Medica	Personalized cellular immunotherapies
186	Machester, UK	Cellular Therapeutics	Cell therapies
187	Manchester, UK	Intercytex	Cell-based products
188	Melbourn, UK	Avita Medical	Autologous skin cell treatment, drug delivery
189	Vienna Austria	Activartis	Dendritic cell-based cancer immunotherapy
190	Vienna Austria	Aposcience	Treatments composed of mixture of cytokines, growth factors, and other active components
		China	
191	Admiralty, China	Cellular Biomedicine Group	Cell therapy
192	Nanjing, China	Nanjing Legend	Small molecules, CAR-T
193	Shanghai, China	Cellular Biomedicine Group	Cell therapy
194	Taipei City, Taiwan, China	Taiwan Bio	Allogeneic mesenchymal stem cell therapy

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
195	Beijing, China	Jieya Laifu Biotechnology	J-1 allogeneic acellular dermal matrix: To repair oral mucosal defects, soft tissue defects.
196	Beijing, China	Jieya Laifu Biotechnology	Allo derm: To repair defect of human derma
197	Beijing, China	Qingyuan Albert Tissue Engineering Biological Technology	Rhino (acellular dermal matrix medical tissue patch): To repair oral mucosa and soft tissue defects
198	Chongqing, China	Zongshen Junhui Biotechnology	Artificial skin—gene transfection pigskin: To repair burns and other trauma wound coverage
199	Qidong, Hunan, China	Oriental Medicine Research Institute	Acellular dermal matrix dressings: To repair superficial II degree burn wounds
200	Shaanxi, China	Eyre skin Biological Engineering	To repair deep II degree, burn wounds, not more than III degree burn wounds 20 cm^2
201	Zhenghai, China	Biotechnology Yantai Zhenghai: Skin Repair Film	To repair various causes dermal wound repair defects.
202	henghai, China	Biotechnology Yantai Zhenghai: Biofilm	To repair a variety of causes dura (spinal) membrane defects
203	Zhenghai, China	Biotechnology Yantai Zhenghai: Dental film	To repair various causes shallow intraoral soft tissue defect repair
204	Guangdong, China	Biological Technology of Guangdong Grandhope	General thoracic surgical repair film
205	Guangdong, China	Biological Technology of Guangdong Grandhope: Sterile Biological Care Record Film	Skin burn, burn and trauma, skin defects
206	Guangdong, China	Biological Technology of Guangdong Grandhope: Biotypes Dura (spinal) Membrane Patch	To repair hard brain (spinal) membrane defect
207	Beijing, China	Datsing Bio-Tech: Allogeneic Bone Grafts	Dental implants, to repair broken bones and bone that has not yet healed

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
		India	
208	Bangalore, KA	Stempeutics	Stem cell—based products
209	Delhi	StemGenn Therapeutics	Stem cell products/therapies
210	Gurgaon	APAC Biotech	Immunocellular therapy
211	Noida, UP	Advancells	Stem cell treatments
212	South Delhi	NutechMediworld	HESCs therapy
213	Delhi	Reliance Life Sciences	Stem cell therapies
214	Delhi	Life Cell	Stem cell therapies
215	Delhi	Cryobanks India	Stem cell Therapies
216	Delhi	Trans-Scell biologics	Stem cell therapies
		Japan	
217	Ibaraki	DNAVEC	Viral vectors and gene therapy
218	Osaka	AnGes	Gene therapy
219	Tokyo	AnGes	Gene therapy
220	Tokyo	Cytori Therapeutics	Cryopreservation systems, cellular therapy
221	Kyoto	Megakaryon	Mass production of platelets from iPS cells
222	Kyoto	ReproCELL	Commercial iPSC products; human iPSC-derived cardiomyocytes
		Israel	
223	Jerusalem	Cell Cure Neurosciences (BioTime)	Cell therapy
224	Jerusalem	Gamida Cell	Stem cell therapy
225	Kfar Saba	Cellect Biosciences	Regenerative medicine
226	KiryatAryeh,	BrainStorm Cell	Autologous, adult stem cell therapy
227	Israel	Therapeutics	Technology
228	Ness Ziona	Kadimastem	Stem cell therapeutics
		South Korea	
229	Seoul	Eutilex	T cell and antibody therapies
230	Seoul	MEDIPOST	Stem cell technology and regenerative medicine
		Singapore	
231	Singapore	Human Longevity Inc	Genotype/phenotype database for therapeutic/diagnostics discovery
232	Singapore	Cell Research Corp	Cord blood stem cells and products

Continued

Table 12.2: List of the companies dealing in field of tissue engineering and regenerative medicine worldwide [143].—cont'd

S. No.	Location	Company	Specific field
New Zealand			
233	Auckland	Living Cell Technologies	Regenerative medicine
Brazil			
234	São Paulo	PluriCell	iPS cells
Malaysia			
235	Cyberjaya	CryoCordSdnBhd	Cord blood and stem cell banking
236	Kuala Lumpur	Stem Life berhad	Cord blood and stem cell banking
237	Kuala Lumpur	Stempeutics Research Sdn. Bhd.	Therapeutics and therapy in regenerative medicine
238	Kuala Lumpur	Cell Safe International Sdn. Bhd.	Cord blood stem cell cryogenic preservation services
239	Kuala Lumpur	Stemtech Sdn. Bhd	The stem cell nutrition
240	Kuala Lumpur	Cell Tissue Technology Sdn. Bhd	Tissue-engineered and cell-based products

even full trachea have been implanted in patients; however, the processes are still at the experimental stage and are not cost-effective. The future potential of this new field has revolutionized the field of medical and health sciences and may improve the economic benefits [102,105]. The profit potential of market for regenerative medicine is expected to reach up to US $67.5 billion by 2020 [105].

7.1 Skin grafts

The use of skin grafting is widely known and has adopted the method of TERM. In combination with various reliable and keratinocyte culture techniques, the epithelial sheets [also called as cultured epithelial autografts (CEA)] formed from a small skin patch have been used to handle burn wounds [84]. The commercial product, i.e., Dermagraft, has been approved as a dermal substitute used for the management and treatment of diabetic foot ulcer [106]. It is an FDA-approved, bioengineered human dermal substitute, and benefits to reestablish the compromised DFU dermal bed to facilitate healing by providing a substrate over which the patient's own epithelial cells can migrate to close the wound [107].

7.2 Cartilage

Carticel (a Genzyme product) is the only autologous arthroscopic cartilage tissue regeneration therapy presently approved by the Food and Drug Administration (FDA) [108].

Genzyme's Carticel procedure, in which chondral cells are excised, cultured and then reintroduced to repair the cartilage defects in patients, at the moment, is the most used in tissue engineering application [109].

7.3 Bioengineering of the body organs

As the day-by-day population is increasing globally, the demand for body organs is also increasing. The TE and RM are only the option and in coming time would be able to fulfill this challenge [110]. The translational application of tissue engineering has engineered the replica of body organs such as heart, liver, lung, kidney, and even a full trachea for implanting into recipients or patients. These bioengineered products work effectively and have improved the life expectancy of the person.

7.4 Natural or accidental damage to body

Life-threatening serious damages, which may occur either because of traumatic episode or natural condition during birth such as congenital anomalies, can be easily regenerated by the application or translational products of tissue engineering [111]. The effects have been well documented and are visible to the recipient as it unfolds the enormous potentials to patients, especially to those with unmet medical conditions. In the year 2020 till now, the FDA has received around 200 applications of the new drugs in lieu of tissue engineering [111].

7.5 Sports medicine

Each year, approximately more than 6 million people visit hospitals in the United States alone for knee, wrist, and ankle problems [111]. The deformations in the bones (extra and intra part of the bone) after the serious injury may lead to potential severe diseases such as osteoarthritis or degenerative joint disease [112]. These types of defects were earlier treated by using autografts and allografts. Autograph often produces problems such as morbidity and limited cartilage tissue availability in the patient site [113], whereas allograph is used in the immune-associated problem [114]. In some of the cases, biomimetic tissue substitutes generated by tissue engineering are helpful.

7.6 Partial or total joint replacements

In many of the difficult situations, where individuals develop rare diseases or conditions or meet with traumatic accidents, amputation or removal of the body or organs is the choice of saving life. In such cases, whole or partial joints/organs/tissues are done to restore or save the life. An artificial implant composed of a metal shell (such as stainless steel or its alloys and titanium), a polymer piece (such as polyethylene glycol to glide

smoothly), and a metal stem are implanted to substitute the damaged joint. An increase in life expectancy years has also demanded the generation of laboratory-based tissue or organs for large populations where the knee or hip replacements are required at large scale. However, due to frequently reported complications, including infection, implant loosening, osteolysis, implant wear and tear, and relatively short life spans of current implants, revision surgeries are often a compulsion, which burdens the patient with higher pain and health insurance costs [115].

7.7 Organ-on-a-chip

Organ-on-a-chip is a recent advanced application of the tissue engineering. A microlevel devices or tools work in an intricate approach to reproduce and reconstitute as replica of tissue interface resulting to functional organ, thereby expanding the cell culture potential into low-cost alternative of animal and clinical studies. Approach has made possible microfabricate models of blood vessels [116,117], muscles [118], bones [119], airways [120], liver [121–124], brain [125,126], gut [127], and kidney [128,129]. But the exact functionality of the organ system has not been achieved because of the complexity and failure to maintain the composite physiological organ–specific microenvironment.

7.8 Treatment of cancer by using multidimensional models

Treatment of early and advanced cancer is well achieved by using these models (3D or 4D) as compared with two-dimensional or monolayer culture. The two-dimensional monolayer lacks the structural architecture, which makes significant limitations. Multidimensional models are good enough to deliver and replicate the elements of a tumor microenvironment such as hypoxia, necrosis, angiogenesis, and cell adhesion topology reasonably and accurately [130]. Multidimensional model was first used by A Carrel in the year 1912. Carrel was capable to culture an explant from a chick embryo and maintained it for 3 months. Furthermore, Leighton developed the system proposed by Carrel, by culturing the tissues on a substrate (sponge matrix) [131–133]. Later, many studies supported the advancement by using these model systems for treating cancer or tumor. However, a much more advanced approach of the 3D culture system, i.e., histoculture offers various advantages such as 3D growth, maintenance of organization and structure, interaction with stromal elements, drug sensitivity testing for individualized cancer therapy, tumorigenicity, and differentiation of cancer stem cells (CSCs) in in vitro conditions [134,135]. However, even after decades of research on these subjects still, research of 3D models is limited in studies due to limitations in standardized testing and analysis procedures and their higher cost of the development, regulation, reproducibility, and commercialization [136]. The challenges such as reproducibility and development might be overcome by the recent development of emerging technology such as

microfluidics and use of the high-end computational and mathematical approaches. However, there is a long way to go in such model systems to be used as a conclusive tool for the regenerative medicine. In the future of the medical science, for early and precise cancer diagnosis, it might be an alternate option as a standard practice to screen the human being against chemotherapeutics and radiotherapeutics.

7.9 Personalized medicine

TERM has been facilitating the personalized medicine depending on the circumstances of the patient's genetic and medical profile. Application has been used in treatments of the ailments such as osteoarthritis, chronic liver failure, heart failure, arrhythmia, wound healing, skin fibrosis, periodontal disease, bone disorders, or blindness [137,138].

7.10 Tissue engineering and regenerative medicine in basic and medical research

Multidimensional organ culture such as 3D and 4D creates a replica of biological environment, which helps to grow and interact with its atmosphere in all the directions, making the model more accurate to mimic in vivo cellular compartment as compared with single or monolayer cell culture system. Therefore, these 3D and 4D model systems are being used for personalized medicine and for studying the effects of drugs and toxic compounds on the cells, mutagenesis, and carcinogenesis; in drug screening and development, additionally capable to reproduce consistent results. These models or systems may be used for research in patient care and training for the graduate student during the medical training. Furthermore, the teaching and research by using animal models may also be replaced, which is an important aspect in terms of social and ethical perspective. Still, these are limited by restrictions such as performance, sensitivity, and compatibility with high-throughput screening instruments.

Hitherto success of TERM is well accepted; nevertheless, it is still standing at unmet clinical need. One of the major issues is that the generated replica still is not meeting its cent percent condition in in vivo conditions such as vascular pressure without leakage or aneurysm formation. However, some of them are successful in animal experimentation studies. Secondly, selection of the biomaterial is very important, as the materials must comply with acceptable bodily parameters or must exhibit as a gold standard material as clinically acceptable biomaterial template. The novelty and coexistence of interdisciplinary subjects' in-depth knowledge of multiple fields with high-skill caliber is required to formulate a successful translational product. However, even after meeting with challenges TE has achieved various successful products, but still the next hurdle is an industrial partnership complying with the international standards or certification (Fig. 12.4).

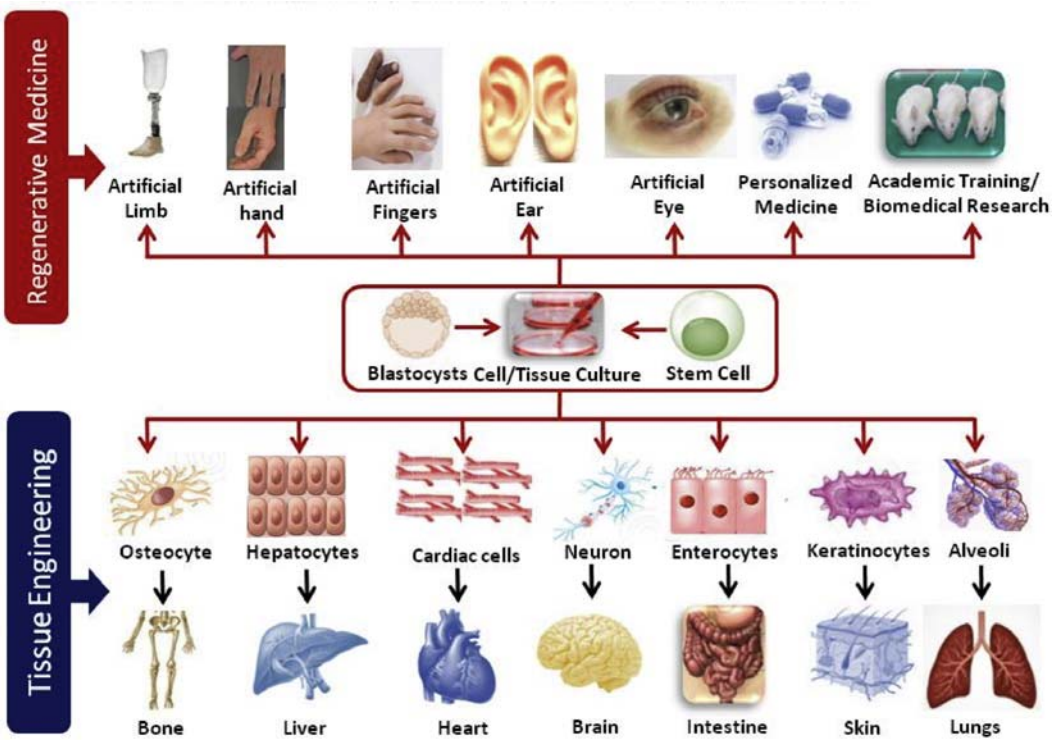

Figure 12.4
Different applications of tissue engineering in regenerative medicine.

8. Regulatory affairs in tissue engineering and regenerative medicine

The trios of science, engineering, and industry have shown the way a wide segment of opportunities in the TERM [139]. These have provided notable benefits in terms of patient care (cancer, chronic wound healing, and transplant of organs in case of organ failure), medical advancement (travel medicine, sport industry), and longevity of humans.

The government in every country has enacted various regulatory, advocacy, monitories, and control agencies to curb the misuse and overuse of the products being utilized for the regenerative medicine and tissue engineering in view of the precautionary principle (Table 12.3). Moreover, since the development at laboratory scale, validation, and marketing, it involves different regulatory frameworks and guidelines, which often makes the inventor a bit confused which guideline or certification must be followed. Thus, the shift in the clinical translation of innovative products has forced the establishment of the novel and inclusive regulatory and monitoring system by regulatory agencies so that the development and marketing of TE products may be achieved jurisdictionally. Two important drivers that enforce the basis and functioning of the regulatory affairs are

Table 12.3: Selected regulatory agencies, countries, and their aim worldwide.

Region/ Country	Agency	Formulated year	Principle aim	References
India	Central Drugs Standard Control Organisation (CDSCO) under Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Government of India	Works under Drug and Cosmetics Act, 1940	To ensure safety, efficacy and quality of the medical product manufactured, imported, and distributed in the country. CDSCO along with state regulators is jointly responsible for grant of licenses of certain specialized categories of critical drugs such as blood and blood products, I. V. Fluids, vaccine and Sera.	[151]
Australia	Therapeutic Goods Administration (TGA) under Department of Health of the Australian Government	1989	To regulate therapeutic goods (including medicines, medical devices, gene technology, and blood products). Tissue–based products under Australian Regulatory Guidelines for Biologicals (ARGB).	[152]
Canada	Health Canada	1993	Regulatory body responsible for the oversight of therapeutic products within Canada.	[153]
Canada	Medical Device Regulation (MDR): For Medical devices	2017	To regulate the sale and advertising for sale of a medical device, and to regulate importation of a medical device for sale or for use on individuals, other than importation for personal use.	[154]

Table 12.3: Selected regulatory agencies, countries, and their aim worldwide.—cont'd

Region/ Country	Agency	Formulated year	Principle aim	References
European Union	European Medicines Agency (EMA)	1995	To regulate tissue-based products, so called as advanced therapy medicinal products, i.e., somatic cell therapy medical products, gene therapy medical products, tissue engineered products, or combined advanced therapy medicinal products, by EMA. Marketing authorization for product may be sought for throughout Europe as a single application called as Marketing Authorization Application.	[153]
Japan	The Pharmaceuticals and Medical Devices (PMD) Act, the Act on the Safety of Regenerative Medicine (ASRM or RM Act), and the Regenerative Medicine Promotion Act.		To regulate the regenerative medicines/ products.	[155]
Japan	Pharmaceutical Affairs Law	2002	To regulate therapeutic products.	[145]

enforced in considering guidelines by concerned agencies. The first is to use the autologous cells in comparison with allogeneic cells, and the second is the use of embryonic stem cells. The later one is of less choice because it couples with many social and ethical considerations while the first one is of the good choice for commercial giants. However, the application of autologous cells has been well documented in orthopedic and dental applications. The area of stem cell research is bound under various social and ethical obligations, wherein stem cell or type is accepted, which is not accepted in view of regenerative medicine. In India, different fields of the stem cell are based on the source and nature of the experiments (Table 12.4).

Table 12.4: Different area of the stem cell research in India based on the source and nature of experiments.

Acceptability of stem cell research areas	Core research area in view of the regenerative medicine
Accepted	• Established pluripotent stem cell line in vitro study or study involving fetal/adult stem cells • in vivo studies in experimental animals (other than primates) with established cell lines (pluripotent stem cells or fetal/adult somatic stem cells) • Establishment of new human embryonic stem (hES) cell lines from embryos left unutilized in IVF program or induced pluripotent stem (iPS) cell lines • Establishment of umbilical cord stem cell bank
Partially accepted	• Creation of a human zygote by IVF, SCNT, or any other method with the specific aim of deriving a hES cell line for any purpose • Clinical trials sponsored by multinationals involving stem cell products imported from other countries • Research involving introduction of pluripotent cells into animals including primates, at embryonic or fetal stage of development for studies on pattern of differentiation and integration of human cells into nonhuman animal tissues • Studies on chimeras where stem cells from two or more species are mixed and introduced into animals including primates, at any stage of development, for studies on pattern of development and differentiation • Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the hES cells were derived is readily ascertainable or might become known to the investigator
Not accepted	• Any research related to human germ line genetic engineering or reproductive cloning • Any in vitro culture of intact human embryo, regardless of the method of its derivation, beyond 14 days or formation of primitive streak, whichever is earlier • Transfer of human blastocysts generated by SCNT or parthenogenesis or androgenetic techniques into a human or nonhuman uterus • Any research involving implantation of human embryo into uterus after in vitro manipulation, at any stage of development in humans or primates • Animals in which any of the human stem cells have been introduced at any stage of development should not be allowed to breed

Framing single-window guidelines, policy for tissue engineering products or devices is difficult, as these products, methods, and devices are quite complex because of its high diversity during development, formulation, and marketing. There are options for wider choice of the available products, and many jurisdictions do not have a worldwide adapted legislation. Thus, universal guidelines without inadequacy or limitations are still a challenge. Besides, technicality of regulation is complex by the fact of using different

approaches by different countries depending on the jurisdiction in which the tissue-engineered product is intended for market. However, directly or indirectly, various international agencies and organizations such as World Intellectual Property Organization (WIPO), World Trade Organization (WTO), World Health Organization (WHO), Pan American Health Organization (PAHO), and International Conference on Harmonization (ICH) are also vigilant for regulation of similar concerns. The US FDA is one of the agencies which has framed and emphasized in the TERM regulatory guidelines since long back. The United States and several countries of the European Union have devised a regulatory framework, and subsequently practicing the specific regulatory law is being developed. Although in France, there is no inclusive regulated enforcement or process for tissue-engineered products derived from human origin, it is requisite to have permission as clinical studies before its approval. The tissue banks recognized by the government of France have control of import of medical devices containing human-derived material. Similarly, Spain also follows the regulatory framework like France, wherein cells, tissue, or tissue-engineered products are to be sourced from approved tissue or cell banks. Two parallel regulatory regimes have been practiced in China, which apply to transformation to the clinic of TERM. They are not mutually exclusive regulations. In the United Kingdom, the body is known as the Medicines and Healthcare Products Regulatory Agency (MHRA). It came into existence in 2003 because of fusion of the two diverse but quite similar agencies, i.e., Medical Device Agency (MDA), responsible for regulation of medical devices, and Medicines Control Agency (MCA), responsible for regulations for medicine [103]. The prime function of the MHRA is to strengthen public protection in context to growing numbers of products that cross the borderline between medicine and devices. However, it is difficult to update and monitor the growing products of TERM as consideration is changing rapidly in recent time. These control bodies are necessarily important during the earliest steps in the product development as it is crucial to ensure the compliance of the quality, efficacy, and safety standards during their development and legal administration [140,141]. However, tissue engineering—based "products" creates greater risk as compared with the "medical devices"; furthermore the associated risks are difficult to assess [142]. Despite much of the research being done worldwide, as of now only a few products are being commercialized and marketed universally (Table 12.2) [143].

A strong regulatory consideration must be formulated for the TERM such as blood, blood products, cells, cellular structure (2D or 3D configurations), and tissue-based secondary products. Framing effective and ideal vigilance and surveillance system in TERM will solve the compliance of quality, efficacy, and safety standards throughout their development, administration, social, and ethical concern. Thus, a holistic regulatory guideline is much needed, which facilitates the regulatory guidance for other countries as well.

9. Conclusion and future perspective

The role of tissue engineering is imperative in the biomedical sciences because of its concealed potential to transform and develop the sphere of the medical field immensely ranging from wound healing to whole tissue or even organ replacement [144]. The tissue engineering in medicine has coined a new term, i.e., regenerative medicine, radically a groundbreaking foundation in the future as far as concern with applied medical science. Since inception, it has demonstrated tremendous possibilities to differentiate the application, methods, products, and substitutes for restoring, augmenting, and maintaining the body (organ and tissue) function in injured or diseased individuals. The generation of iPS cells has improvised personalized medicine. Patient-specific customized tissue or graft is now well devised and accepted by the host immune system because of its advancement in the field, such as biomaterials, source cell type, bio fabrication technologies, and self-assembled or programmed organogenesis. Biomimetic tissue has been generated through biomaterials and scaffold architecture to mimic the body parts and their primary functions. There are various products such as artificial heart, kidney, skin, retina, cartilage tissue, customized organs, and prosthetics that have been produced in the laboratory via biomaterials and have been commercialized and marketed worldwide. There are a wide variety of the tissue engineering products of medical importance, such as kaloderm (2 degrees burn), holoderm (2 degrees and 3 degrees burn), diabetic foot ulcer (second approval), JACC (steochondritis dissecans), JACE (severe burn), MACIa (cartilage defects with or without knee), carticel (cartilage defects of the femoral condyle), and GINTUIT or allogeneic cultured keratinocytes and fibroblasts in bovine collagen (topical treatment for postsurgery vascular wound healing with mucogingival conditions in adults), which has been under commercial production and available in the market. Furthermore, several biomaterial-based products exhibited promising outcome at the laboratory as well as in clinical pilot studies. Three-dimensional bioprinted construct and a scaffold model of human importance has further advanced the quality and expectancy of life. Now, it is well known that the innervation and vascularization play a pivotal role as an important driver for tissue and organogenesis as well as a means for their controlled functional modulation. Various body organs, such as blood vessel [145] bone marrow [146], intestine [147], kidney [148], lung [120,149], and liver [150] have been developed on a material substrate as organ-on-chips. Even after attaining many milestones in tissue engineering at various levels, including laboratory studies, animal research, marketing, and commercialization of the product, still we are missing the imperative link such as availability of appropriate cell types and inability to generate large and vascularized tissue that can be easily integrated with host's circulatory system. Tailoring of the functional cells makes them compatible immunologically to comply with immune system for better and early acceptance of prosthetic or the transplant, and multidimensional architectural complexity between hosts and newly implant body part. Such issues are exceptionally crucial to use the tissue engineering methods or products in medical sciences. Furthermore, the transition from

laboratory to patient bedside, tissue engineering product marketing, and compliance of social and ethical guidelines at national and international platforms compound the limitations of the field. Thus, in lieu of pit-and-falls, we anticipate the innovation and development in diverse subject, such as chemical, materials, physical, biomedical, engineering, immune nanotechnology, stem cell, genetic editing, biofabrication and computational sciences will aid revolutionary path-breaking potential for bionanomaterials in regenerative medicine to meet the future needs of the medical sciences.

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CHAPTER 13

Bionanomaterials for cancer therapy

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1. Introduction

Cancer is the malignant and abnormal growth of cells, being the second reason leading to killing more than 9 million people annually across the world. This number stands for one in six deaths worldwide because of cancer approximately. The most common therapies for this disease are chemotherapy, radiotherapy surgery, and hormone therapy [1]. Despite the side effects of radiation therapy, this strategy is essential for treating half of the patients with this disease [2,3]. Although chemotherapy's strong anticancer effects are due to cytotoxic drugs' nonselective action and the targeting of cancerous and healthy cells, much toxicity is unfortunately distributed within the patient's body treatment. Therefore, with this type of treatment and after, it is evident that getting rid of the long-term devastative effects of heart toxicity, neurological disorders, infertility, nephropathy, and chronic liver damage will be inevitable [4–8].

A way to improve these devastative effects of cancer drugs is to include various advanced drug delivery systems in encapsulation and nanoparticle loading application. It can be performed by releasing and controlling the drug with minimal or even no toxicity to the tumor site. Research has focused on killing cancer cells by targeting them and maintaining healthy cells. New carriers for achieving this aim have been designed for anticancer drugs that bring the drug to its intended location by more accurately identifying the target [9].

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Among these, nanoparticles have received more attention because they have a more straightforward production method and can be prepared through biocompatible polymers. Because of the more incredible permeability of the vessels around the growth tissue than the ordinary tissue vessels and because of the quick development of the requirement for more oxygen and supplements, malignancy cells will want to ingest better medications because of the improved penetrability and maintenance (EPR) wonder [10,11].

Nanoparticles discussed in this chapter can be well used in drug delivery. In previous years, drug-carrying nanostructures' ability, control, and access to authorized drug molecules have also been made possible. Over the last half-century, advances in related sciences, such as polymer and chemistry, biology, as well as mechanics, and physics, have all been able to influence the diversity of nanocarriers and the various categories of carriers, and they could introduce to medical science with unique characteristics and other performance [12]. Among the applications of nanostructured materials in drug delivery systems (DDSs) include drug carriers in diseases, such as cancer, cardiovascular disease, and Alzheimer's disease [13].

The primary purpose of designing a helpful DDS using technology is to target the drug to specific cells or tissues, increasing its therapeutic effects, reducing its therapeutic dose, and modifying biocompatible nanomaterials for drug delivery [13].

2. Cancer disease: types and statistics

Development of healthy cells into cancer cells is a condition that usually proceeds from a precancerous lesion into some malignant tumor cells. Cancer is the world's second-highest source of death, reported at 9.6 million fatalities in 2018. Approximately one in six cancer deaths worldwide are due to cancer. In low- and middle-economy countries, approximately 70% of deaths from cancer arise. The International Cancers Research Organization (IARC) reports that 1 out of 5 men and 1 out of 6 women in the world grow cancer over their lives and that 1 out of 8 men and 1 out of 11 women are killed by their illness, as shown in Fig. 13.1.

Cancerous cells vary in several respects from normal cells because they become unregulated and aggressive. An essential distinction is the reduced specialization of cancerous cells than usual. Although regular cells grow into many different types of cells with distinct roles, cancerous cells should not. As mentioned earlier, it is another reason why cancer cells start to split without stopping, unlike healthy cells. Cancer cells are often capable of missed signaling that cells typically avoid separating or initiating a mechanism programmed cell death or apoptosis, which the body uses to clear unwanted cells. More than 100 tumor forms occur. Cancer forms are typically named by the tissues or organs in which cancer occurs. For instance, lung cancer occurs in lung tissue, and brain cancer

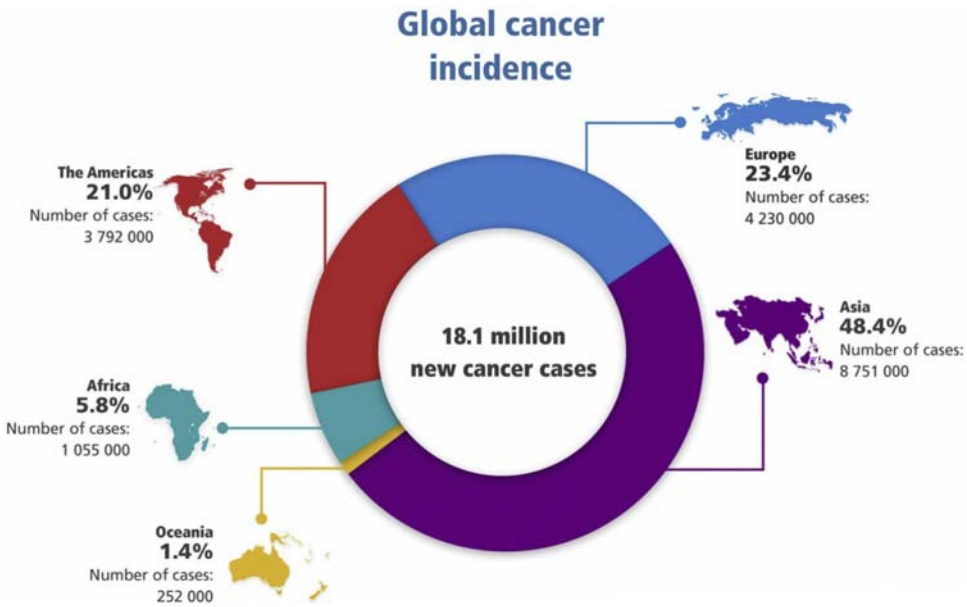

Figure 13.1
Estimated percentages of the reported number of cancer cases distributed worldwide as the International Agency for Research on Cancer (IARC) reports in 2018. *source @IARC GLOBOCAN 2018.*

begins in brain cells, as depicted in Fig. 13.2. Cancer can be categorized into four main categories: (1) the most prevalent form of cancer is carcinomas. They consist of epithelial cells, which cover the body's [14] inner and outer layers. Several different types of epithelial cells also come underneath a microscope as columns (2) sarcomas are bones and soft tissue tumors, comprising muscle, fat, arteries of the blood, lymph vessels, and fibrous tissue (such as ligaments and tendons [15]). (3) Leukemias are classified as tumors starting in bone marrow blood-forming tissue. Muscular tumors are not produced in these cancers. Afterward, the blood and bone marrow got to be overflowed by an endless sum of unusual white blood cells (leukemia and leukemia impact), padding solid blood cells. The low rate of healthy blood cells will make it increasingly challenging for the body to obtain oxygen, regulate inflammation, or combat pathogens [16] (4). Lymphoma would be a lymphocytic cancerous tumor that begins with (T cells or B cells). These are white blood cells that combat disease and contribute to the immune response. In lymphoma, the lymph node, lymphatic vessels, and other bodies are damaged by irregular lymphocytes [17].

3. Anticancer nanocarriers

In general, drug carriers can be classified into two main groups: (1) organic carriers, including ceramic NPs, metal NPs, and carbon NPs, and (2) inorganic carriers include

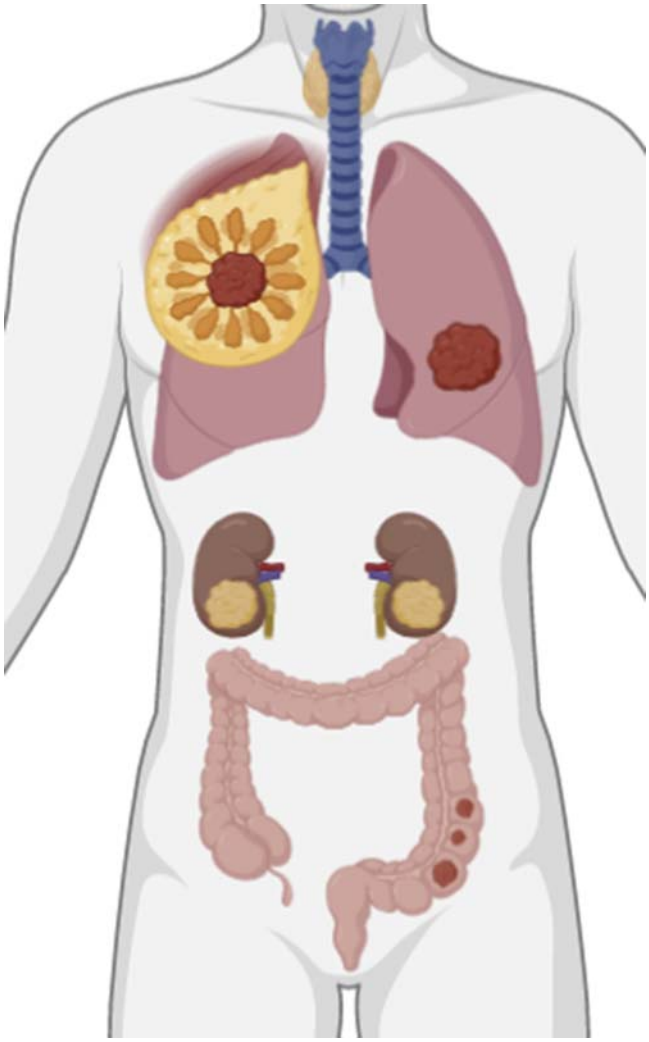

Figure 13.2
Common cancer types, such as lung, breast, colorectal, esophagus, and kidney cancers due to distinct factors [18].

liposomes, solid lipid nanoparticles (SLNs), polymeric micelles (polymeric micelles), dendrimers, polymersomes, hydrogel NPs, and biodegradable polymers [19–22]. The most common materials in drug delivery in the form of nanoparticles are polymers. Polymer nanoparticles (PNPs) are defined as colloidal particles with sizes between 10 and 1000 nm [23]. Moreover, they are composed of natural (chitosan, gelatin, sodium alginate, and albumin) [24–27] or artificial biodegradable polymers, such as polylactic acid (PLA), polyglycolides (PGAs), poly(lactide co-glycolides) (PLGAs), polyanhydrides,

polyorthoesters, polycyanoacrylates, polycaprolactone, polyglutamic acid, polymalic acid, poly(*N*-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, poly(ethylene glycol) (PEG), and poly(methacrylic acid) [28–39], which is biocompatible and nontoxic; more examples are depicted in Fig. 13.3.

Biocompatible and nontoxic are common characteristics of natural polymer nanoparticles; however, their low solubility has limited application, when offered in various biological membranes [40]. Such delivery exposes the nanoparticles to various pHs. This change in pH and some other issues sometimes restrict their use. Features such as biocompatibility are required for potential applications in tissue engineering, drug and gene delivery, and new vaccination strategies.

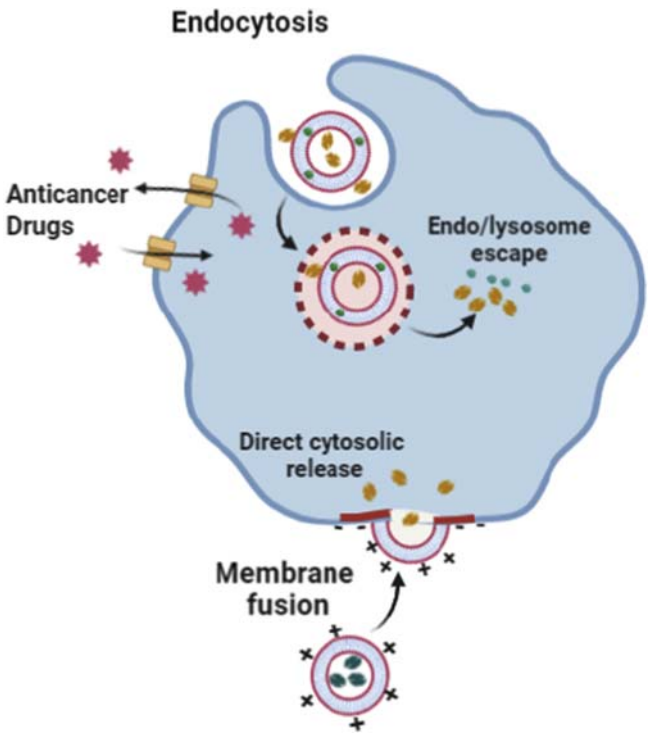

Figure 13.3

Nanoparticle drug delivery system to selectively target the desired cells. Therapeutic agents are loaded into appropriately selected polymer nanoparticles that may enter the target cells through the process of endocytosis and release therapeutic agents inside the endolysosomal effect of the cell cytoplasm. Alternatively, the cationic nanocarriers can fuse with the negatively charged cellular plasma member and release the therapeutics into the desired cells. One of the disadvantages of using nontargeted therapeutics as free drugs is the membrane-active drug efflux pumps that expel the therapeutic from the cytoplasm to the outside of the cell.

3.1 Polymeric nanocomposite drug delivery

PNCs are a combination of different polymers with nanoparticles established themselves as a suitable type of nanocomposite (NC) biomaterials for regenerative medicine as well as drug delivery applications and are widely investigated as multifunctional nanomaterials. These PNCs can be classified into four types with different nanofiller, which are discussed in this section.

3.1.1 Polymer–polymer nanocomposites

Most researchers are currently focusing on polymer-based bioNCs. Their NCs in various forms, such as micelles, hydrogels, polymers, and liposomes, play an essential role in treating cancer with unparalleled design capacity, environmentally friendly nature, and comfortable and cost-effective production. PNCs are composed of polymers and nanomaterials in various types, shapes, and sizes. The interaction of the polymer matrix and nanoparticles is significant in determining the hybrid structure's compositional properties. They can provide higher payloads, extended circulation time of drugs, drug targeting, and solubility [18].

PNPs comprise a large group of compounds, including vesicular systems (nanocapsules) and matrix systems (nanospheres) (see Fig. 13.4). The drug is trapped inside a polymer cavity in nanocapsules; however, the drug is dispersed in a polymer matrix [41].

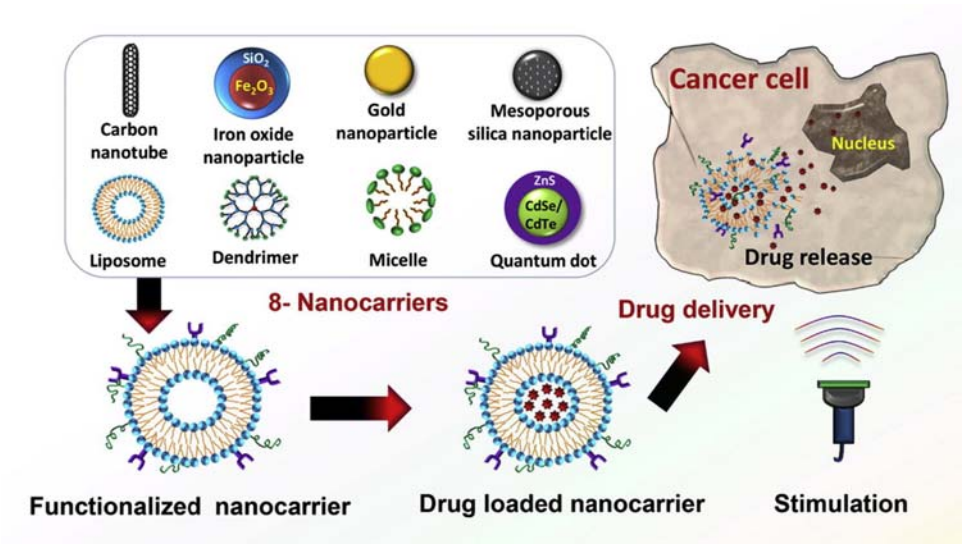

Figure 13.4
Various examples of nanomaterial constructed from various metallic and nonmetallic nanomaterials, mesoporous silica nanoparticles (MSNs), iron oxide nanomaterials, carbon nanotubes, dendrimer, micelle, quantum dots as core–shell nanomaterials and their applications as nanocarriers with surface functionalities for the selective targeting to the target cell, which will lead to the therapeutic release after specific stimulants within the target cell [42].

Abraxane was the first polymer nanoparticle introduced to the world pharmaceutical market in 2005 by American Pharmaceutical Partners and American Bioscience company, which comprised of nanoparticles of the drug paclitaxel, bound to albumin [43,44] (Fig. 13.5). This formulation is fabricated to release a compound called chromophore-EL, present in previous paclitaxel formulations by increasing solubility. Chromophore causes severe allergies in certain patients that can threaten their life. With this great success of Abraxane, it has been proven that nanotechnology can introduce products to overcome the challenges of formulation science.

The hydrophilic layer of polymeric micelles (PMs) with core–shell structure has core–shell PMs due to a hydrophilic shell making them a good candidate as a nanocarrier for loading hydrophobic drugs into the core. Blanco et al. [45] reported the effect of encapsulation of β-lapachone in PEG–PLA NPs on A549 cell lysates and orthotopic

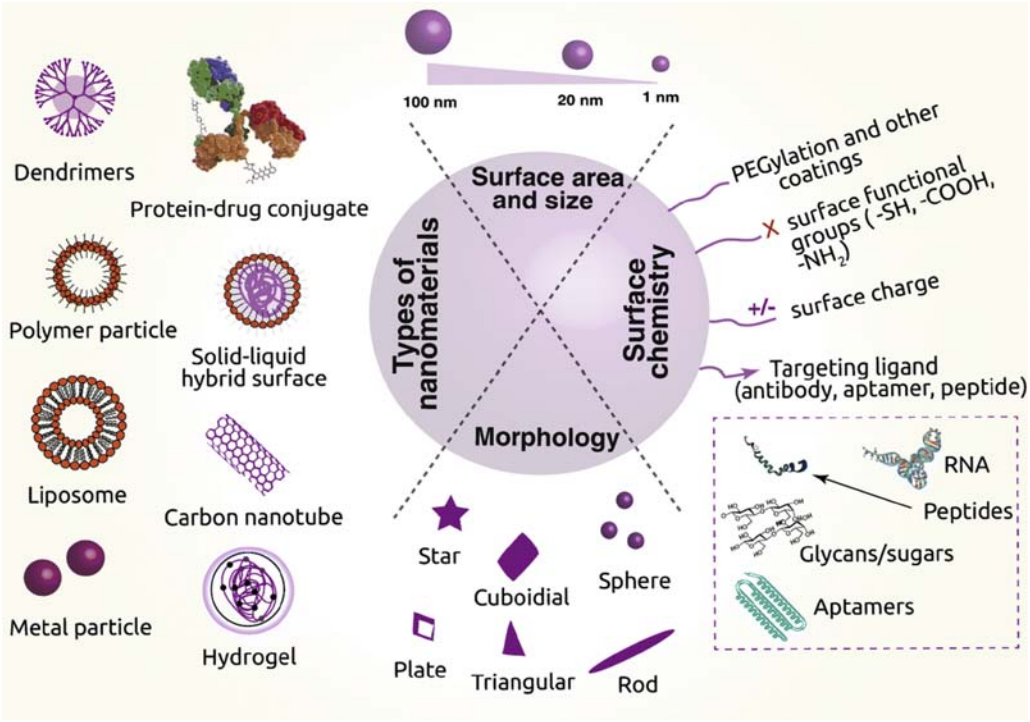

Figure 13.5

The usual surface modifications of polymeric nanoparticles, PEGylation, carboxylate, amine, antibodies, aptamer, peptides, glycans, and surface charge. Generated nanomaterials could be classified as natural nanomaterials, such as proteins, liposomes, dendrimers, and liposomes, and synthetic nanomaterials, including core–shell nanomaterials, hydrogels, carbon nanotypes, and metallic nanoparticles. The obtained nanomaterials vary in their shape from spherical, cuboidal, start, plate, triangular, and rod-shaped with various desired sizes [51].

Lewis lung carcinoma (LLC). The results indicated a drastically reduced tumor growth and metastatic tumor burden when compared with free β-lapachone [45]. In another study, MPEG−PLA and Pluronic were employed to deliver docetaxel [46]. The investigation showed that the volume of tumor size significantly reduced more when treated with mixed micelles. Jun et al. demonstrated that CP570 micelles could be used as a carrier to deliver docetaxel [47]. Their study showed that CP570 micelles did not significantly affect the improvement of the pharmacokinetics of docetaxel. Furthermore, Park et al. compared conjugated and encapsulated PLGA−PEG MPs containing doxorubicin (DOX) [48]. The drug release of the conjugated DOX−PLGA−PEG MPs was more significant than encapsulating PLG−PEG MPs due to gradually hydrolyzing conjugated DOX−PLGA and controlled release water solution DOX−PLGA in the incubation medium. The stable release of DOX from DOX−PLGA−PEG micelles was similarly observed in compounds containing microspheres and prepared PLGA nanoparticles with various hydrophilic drugs to PLGA [49,50]. PNPs surface has been modified with different methods, such as charge modification, bioactive peptides graft, amphipathic compound graft, and siRNA to obtain the appropriate functions to fit the tumor environment or properties of drugs as shown in Fig. 13.5.

3.1.2 Polymeric−magnetic nanocomposites

Magnetic NPs are widely used in magnetic resonance imaging (MRI), biosensors, theranostics, delivery, magnetic hyperthermia, photodynamic therapy, and photothermal ablation therapy [52−58]. However, magnetic NPs, due to aggregation and low stability in biological environments, are often coated with or embedded in a polymer [59,60]. This surface coating has a sufficient role in improving some MNPs' properties such as pharmacokinetics, systemic toxicity and clearance rate, nonspecific protein adsorption or cell interactions, and sustained drug release. Magnetic NP−coated polymers are proposed as new materials for releasing the chemotherapeutic cancer drugs in the desired tissue or organ. Many researchers have extensively studied polymeric−magnetic NCs for innovative triggered release in controlled drug delivery. An overview of polymeric−magnetic NCs for drug delivery applications is listed in Table 13.1 [61].

In addition to chemotherapy drugs, implantable magnetic (Fe_3O_4)-reinforced polydimethylsiloxane NCs for the localized breast cancer treatment via hyperthermia were explored by Kan-Dapaah et al. [76]. It has been identified in the study that the thermal dose coverage influences NC shape and size. Recently, an alternating current (AC) magnetic field has developed a novel fabrication technique for synthesizing spherical microactuators of PLGA/Mg-γFe_2O_3 NCs [77]. The release rate results showed an increased diffusion rate in the excited PLGA/Mg-γFe_2O_3 NCs by the AC magnetic field.

Table 13.1: Distinct polymeric–magnetic nanaocomposites for specific drug delivery applications.

Magnetic nanoparticles	Polymer	Drug loaded/application	References
Carbonyl iron	Poly(butylcyanoacrylate)	5-Fluorouracil Ftorafur	[62]
Fe_3O_4	Starch-g-poly(methylmethacrylate-co-PEG-acrylamide)	Doxorubicin	[63]
Fe_3O_4	Poly(lactic acid)/PEG	Doxorubicin hydrochloride	[64]
Fe_3O_4	APS–PEG–TFEE	Doxorubicin	[65]
Fe_3O_4	PEG-b-poly(4-vinylbenzylphosphonate)	Doxorubicin	[66]
Fe_3O_4@LaF3:$Ce3^+$, $Tb3^+$ nanoparticles	Chitosan	Paclitaxel	[67]
Fe_3O_4	Poly[(*N*-isopropylacrylamide-r-acrylamide)-b-L-lactic acid]	Paclitaxel	[68]
Fe_3O_4	Cisplatin	Heparin	[69]
Fe_3O_4	Chitosan	Gemcitabine	[70]
Fe_3O_4	PEGylated PLGA	Sorafenib	[71]
Fe_3O_4	Chitosan	Bortezomib	[72]
Fe_3O_4	Chitosan	Gemcitabine	[73]
Mesoporous silica	PEG-co-poly(vinyl pyridine)	Doxorubicin	[74]
Fe_3O_4	Chitosan–polymethacrylic acid	Doxorubicin	[75]

The schematic structures of eight biological source-based MNPs as drugs has been approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMEA), Japanese Ministry of Health, and Australia's Therapeutic Goods Administration for different clinical applications and derivatives as shown in Fig. 13.6 [78–81]. Moreover, some other magnetic NP–based drugs including Feraheme, Endorem, Gastromark, Lumiren, Ferumoxytol, Combidex, Radiogardase, Feridex, and NanoTherm have been recently approved by the FDA and European Medicines Agency (EMA) for various applications in iron deficiency, iron replacement therapy, the lymph node metastases imaging, MRI, pharmaceutical contrast agents or oral antidotes for heavy metal contamination in humans, and the treatment of intermittent glioblastoma multiforme [82–84].

3.1.3 Polymer–metallic nanocomposites

Metallic NPs are nanosized metals with dimensions (length, width, or thickness) within the size range of 1–100 nm and can be synthesized in different forms through various

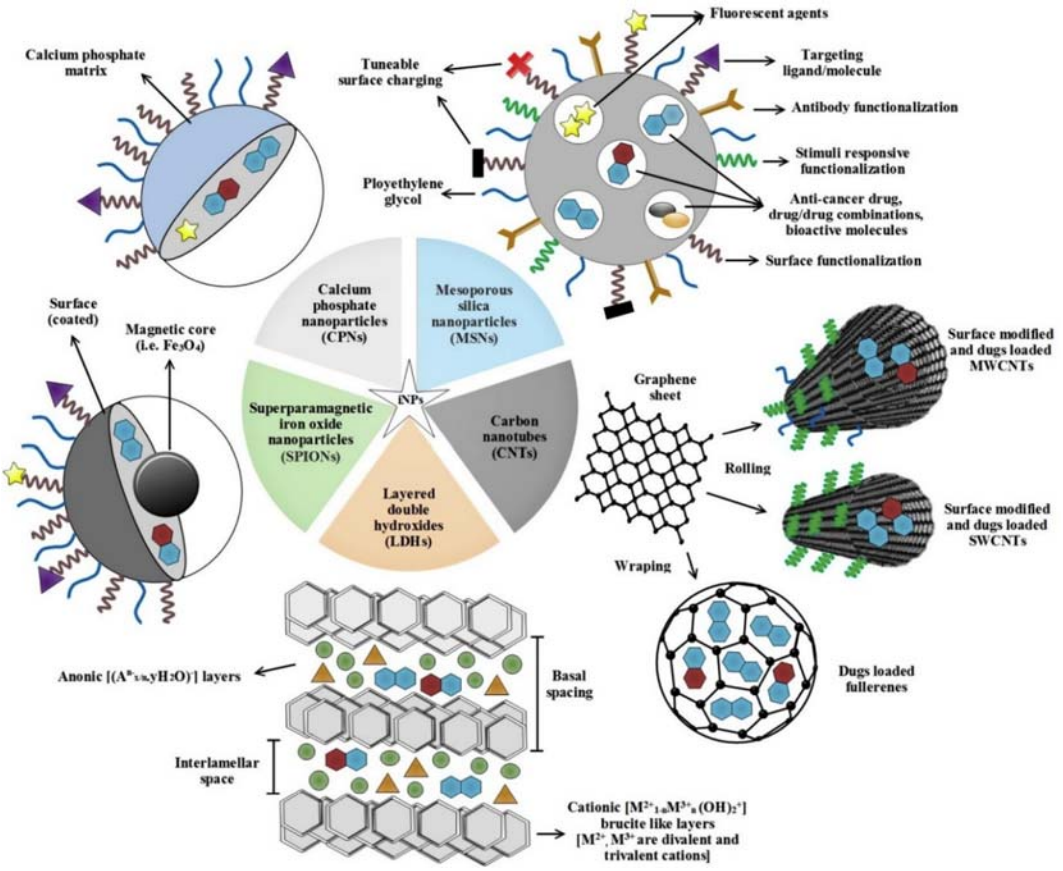

Figure 13.6

Schematic diagram depicting various inorganic nanodrug delivery platforms (NDDPs) loaded with anticancer chemotherapeutic agents employed for cancer treatment. iNPs, inorganic nanoparticles; MWCNTs, multiwalled carbon nanotubes; SWCNTs, single-walled carbon nanotubes [42].

methods [85–88]. Metallic NPs, such as silver (Ag), gold (Au), titanium (Ti), platinum (Pt), palladium (Pd), and copper (Cu), are generally used as drug carriers and contrast agents in cancer treatment [89–91]. The applications of these substances due to their antiproliferative and apoptotic induction properties for use in cancer therapy have been studied by many researchers [92–95].

Tumor blood vessels are often large and have an insufficient lymphatic system [96,97]; therefore, metallic-based NPs can easily penetrate the cancerous cells and kill them. The cytotoxic effects of silver nanoparticles (AgNPs) on the MCF-7 breast cancer cell line were studied in a previous work. The MTT assay results demonstrated a significant reduction of cancer cell proliferation after 24 h [98]. In another work, the effect of silver

(AgNPs) and gold nanoparticles (AuNPs) as an antitumor treatment in vitro against human breast cancer cells (MCF-7) was investigated [99]. The mechanism of cytotoxic effects of silver and gold nanoparticles (AgNPs, AuNPs) on cancer cells is proposed to be due to the increasing disruption of reactive oxygen species (ROS) released by the nanoparticle toward mitochondria. This disruption leads to reduced cellular energy production (ATP), which eventually causes DNA damage and cell death [100,101]. However, it has been used to combine AgNPs with an anticancer drug to get over chemoresistance and undesired side effects of chemotherapeutic drugs. Gopinath et al. investigated the combination of AgNPs and 5-fluorouracil (5-FU) effects on the baby hamster kidney (BHK21) and human colon adenocarcinoma (HT29) cell lines [102]. The study revealed that AgNPs can act as a therapeutic drug and represent a new chemosensitization strategy for future gene therapy applications. Furthermore, the results indicated that AgNPs apoptotic cells' mechanism associated with mitochondrial membranes' damage is same as the mechanism induced by other drugs or gene therapy treatments.

DOX is an anthracycline type of chemotherapy with broad-spectrum activity and is used to treat various cancer types. Hekmat et al. demonstrated that the combination of AgNPs and DOX could alter DNA structure [103]. Moreover, the study identified that the AgNPs and DOX improved the cytotoxic effect of DOX on MCF7 cells and T47D cells compared with stand-alone DOX or AgNPs.

Platinum complexes are another typical metallic NPs that are introduced as cancer treatment agents in 1968, due to various oxidation states, chelating properties, redox potentials, uneven ground, and excited electronic states [104]. Thus, several approved platinum-based drugs by the FDA, Japan, China, and Korea, are used in different cancer treatments as listed in Table 13.2.

Nevertheless, the metallic NPs are unstable in the blood and have low cellular uptake in cancer, limiting their clinical application. Besides, severe chronic kidney disease, neurological disorder, and ototoxicity are the main effects of these materials. Consequently, to overcome these problems, the surface of metallic NPs has been modified with biocompatible polymers and encapsulated of drugs in nanosized drug carries to avoid aggregation of nanosized metal and preserve their properties and increase the duration of drug action without the loss of their volume and activity. On the other hand, inhibition of tumor cells without harmful effects on healthy tissue should be considered [115,116].

The cytotoxicity effect of the conjugated DOX onto core−shell Ag/PNCs was investigated [117]. The core−shell Ag/PNCs consist of AgNPs as a core, and three FDA-approved polymers (PVA, PEG, and PVP) were as a shell. The MTT results showed that DOX/Ag NCs are more cytotoxic to MCF-7 cells than normal 1BR hTERT cells. The results also showed that DOX−Ag/polymeric (PVA, PEG, and PVP) NCs showed IC50 at 10-fold reduced doses than free DOX and DOX−AgNCs. Based on the experimental results, it can

Table 13.2: Applications of platinum-based drugs.

Drugs	Applications	References
Cisplatin	Testicular cancer, ovarian cancer, cervical cancer, breast cancer, bladder cancer, head and neck cancer, esophageal cancer, lung cancer, mesothelioma, brain tumors, and neuroblastoma	[105,108–111]
Carboplatin	Ovarian cancer, lung, head and neck, endometrial, esophageal, bladder, breast, and cervical; central nervous system or germ cell tumors; osteogenic sarcoma; and as preparation for a stem cell or bone marrow transplant	[105,108–110]
Oxaliplatin	Advanced cancer of the colon and rectum	[105,106,109]
Nedaplatin	Advanced or recurrent esophageal cancer	[107,108]
Lobaplatin	Breast cancer, esophageal squamous cell carcinoma, gastric carcinoma, lung cancer, melanoma, and ovarian cancer	[107,113,114]
Heptaplatin	Advanced gastric cancer	[108,112]

be concluded that the efficiency of DOX–Ag/polymeric (PVA, PEG, and PVP) NCs is the same as DOX alone, but with less dose of DOX about 95%. In another study, Venkatpurwar et al. synthesized novel carriers for anticancer drug delivery with capped gold nanoparticles [118]. The result showed a significant enhancement in cytotoxicity of DOX–AuNCs on human glioma cell lines (LN-229) compared with free DOX that can be attributed to the increase of cellular internalization via AuNP-mediated endocytosis. The role of AuNP-mediated endocytosis in the growth inhibition of cancer cells through the release of the conjunction of methotrexate–gold nanoparticles (MTX–AuNPs) inside cancer cells was also reported by Chen et al. [119].

3.1.4 Polymer ceramic nanocomposites

Besides, hyperthermia (HT) is a novel strategy through the local application of heat to inhibit cancer cells. HT is categorized into three groups, such as whole body, regional, and localized. The body temperature in whole-body hyperthermia (WBH) is raised to 39.5 and 40.5°C (103.1 and 104.9°F) [120,121]. Indeed, this temperature is defined between 41.8 and 42°C (107.2–107.6°F) in Europe and the United States, where it is approximately

43−44°C (109−111°F) in Japan and Russia. This method raises the patient's body temperature by immersing in a hot water bath, heating blankets, or ultraviolet radiation. Nevertheless, the body temperature in the case of local/regional hyperthermia remains unchanged. All of these methods have certain side effects, such as pain at the site, infection, bleeding, blood clots, swelling, burns, blistering, and damage to the skin, muscles, and nerves near the treated area, nausea, vomiting, diarrhea, and problems with heart, blood vessels, and other major organs [122].

Hyperthermia based on the combination of polymeric matrix embedding magnetic bioceramic fillers is proposed to solve the challenges in conventional HT. By the hyperthermia method, ferromagnetic glass−ceramics (FGCs) have shown promising outcomes for the treatment of deep tumors, such as osteosarcoma cells [123]. Kokubo et al. synthesized the FGCs granule and showed that when it was located around the tumors, strongly bonding it and bone, a bone-like apatite complex around the tumors is formed [124]. Hence, tumor cells were inhibited due to efficient heat after exposure toward an alternating magnetic field.

As a typical carrier material, ceramic nanoparticles have been extensively exploited for imaging-guided therapy, including silica [125], NIR spectra of 5% Er^{3+}-doped glass−ceramics [126], and lanthanide-doped upconversion nanoparticles (UCNPs) [8−12]. Previous reports indicated that biomacromolecules were closely related to the bioinspired mineralization process. For instance, the mineralization of $CaCO_3$ [127] can be induced and regulated by regenerated silk fibroin (SF)-based nanostructures through an oriented crystallization process [26,27]. A series of magnetic glass−ceramics containing different additions of P_2O_5 or MnO_2 in the system Fe_2O_3−CaO−ZnO−SiO_2−B_2O_3 for localized treatment of cancer was studied by Abdel-Hameed et al. [128,129]. Increasing P_2O_5 or MnO_2 in the composite influences on thermal effect and decreases it. Tumor hypoxia is caused by the rapidly proliferating cancer cells enclosed in the distorted tumor vasculatures, which severely hinders the treatment efficacy of photodynamic therapy (PDT) owing to the insufficient oxygen supply in the tumor microenvironment [28−30]. Significantly, MnO_2 nanoparticles can induce enzymatic decomposition of H_2O_2 into water and oxygen and thus may work as a crucial mediator to diminish tumor hypoxia [34,35]. Furthermore, MnO_2 can decompose in response to other tumor-specific environmental cues, such as glutathione (GSH) or local acidity, and the produced Mn^{2+} is an excellent contrast agent for T1-magnetic resonance (MR) imaging of tumoral tissues [130].

In a recent study, Yang and coworkers clinically confirmed that photosensitizer indocyanine green (ICG) and chemotherapeutic drug DOX were coimmobilized into silk fibroin (SF) nanoparticles, where MnO_2 mineralized the particle surface through a bioinspired crystallization process (Fig. 13.7) [130].

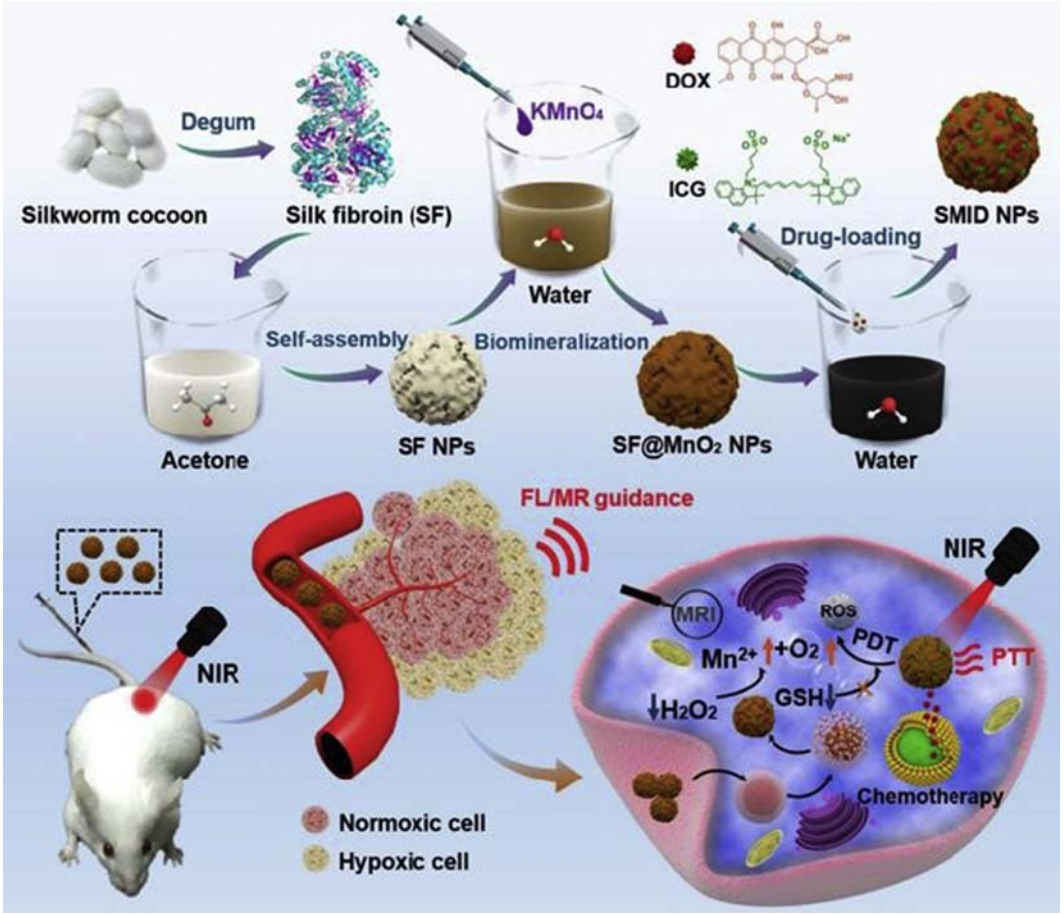

Figure 13.7
Schematic of the synthetic procedure of SF@MnO_2/ICG/DOX (SMID) nanoparticles as a multifunctional drug delivery platform for in vivo MR/fluorescence imaging-assisted trimodal therapy of cancer [130].

Among the different ceramic nanoparticles developed so far, mesoporous SiO_2 has attracted the scientific community's attention for being applied as a drug delivery system capable of controlling the drug release in space and time. Modifications of SiO_2 NPs with different types of polymers were performed so far to imprint them a stimulus-responsive behavior (namely, pH, redox potential, adenosine triphosphate, enzyme, or temperature) to allow their application in cancer therapy, which is schematically represented in Fig. 13.8. Several efforts have been executed via MSNs to target specific tissues through passive or active targeting procedures [131].

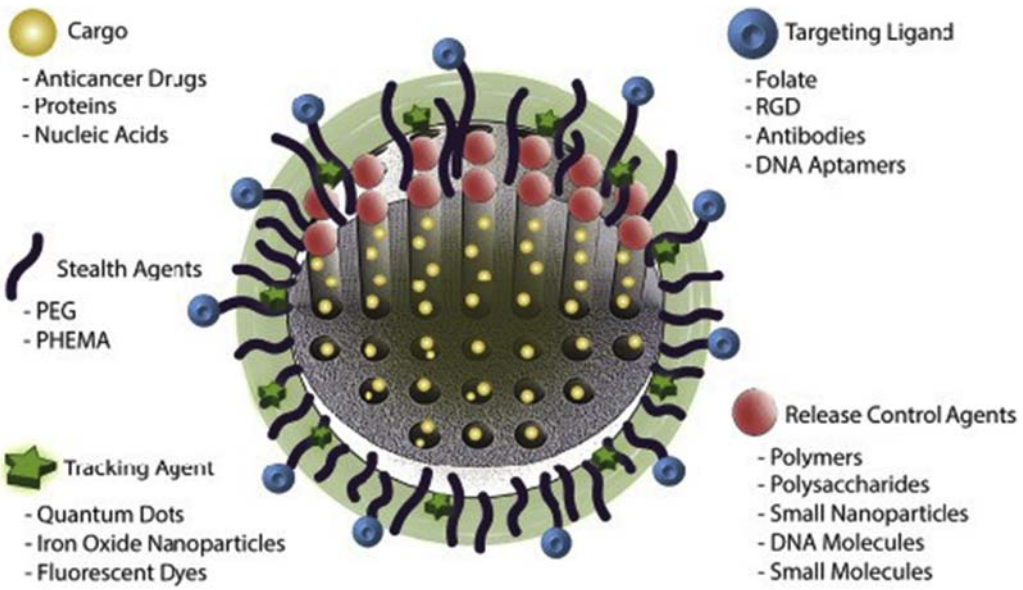

Figure 13.8
Schematic representation shows different stimuli-responsive behaviors of mesoporous silica nanoparticles for cancer therapy [134].

In the beginning, MSNs were developed as an anticancer drug delivery system, mainly based on their efficacy to store a high amount of chemotherapeutics into pores and exploit the enhanced permeability and retention (EPR) effect for passive targeting to tumor tissues. This part of the chapter will discuss the EPR effect and passive targeted cancer therapy using MSNs. Later, MSN surface modifications by conjugating targeting ligands were introduced to enhance MSN uptake in targeted cells. Different targeting moieties have been employed to the surface of MSNs, e.g., small molecules, aptamers, short peptides, antibodies, and antibody fragments [131].

Nasab et al. fabricated chitosan nanoparticles that are coated with curcumin [132]. The results showed that mesoporous silica nanocarriers, refined by chitosan as a pH-responsive polymer, improved curcumin's solubility in the aqueous media and could be acted as a nanocarrier against the U87MG glioblastoma cancer cell line. In another study, a core−shell system containing chitosan−poly(methacrylic acid) (CS−PMAA) shells and MSN cores was studied [133]. According to this study, the drug-releasing and release behavior of loaded DOX hydrochloride−MSN/CSPMAA composite showed high drug-loading capacity encapsulation efficiency 22.3 ± 0.3% and 95.7 ± 2.0%, respectively.

Osteosarcoma (OS) or osteogenic sarcoma (OGS) (or only bone cancer) is a type of cancerous tumor in a bone that is usually found in the long bones around the knee. This type of cancer is found in children, adolescents, and young adult men than women [135].

This type of cancer is found in children, adolescents, and young adult men than women [135]. Among the most common treatments for osteosarcoma are surgery, chemotherapy, and radiation therapy.

Moreover, patients with higher-grade tumors are treated with a new method known as neoadjuvant therapy (chemotherapy given before surgery) in recent times [136]. Apart from the potential clinical benefits of chemotherapy drugs, due to localization of OS in a wide area and cutting off from the blood vascular system resulting from crushing healthy vessels [137], the defective drug reaches the tumor.

Additionally, since OS is spread to other tissues, a sensitive platform to recognize healthy and tumor cells is required. Therefore, polymeric−ceramic NCs have received much attention as a potential basis for one such advanced platform. The novel hydroxyapatite−polyvinyl alcohol−doxorubicin anticancer drug (HAp−PVA−DOX) NC was developed for obstructive sleep apnea (OSA) treatment [138]. It was shown that the DOX−HAp−PVA NC is highly toxic toward osteosarcoma cells (MG 63) with better biological properties. Son et al. developed drug-loaded calcium phosphate (CaP) NC system containing an anticancer drug, such as caffeic acid (CA-NP), chlorogenic acid (CG-NP), or cisplatin (CP-NP) in the presence of alginate as a polymer template to control the release rate of drugs for overall survival (OS) treatment [139]. The anticancer activity of cisplatin-loaded CP-NP NC was higher than another NC on OS and dependent on drugs and time concentration overall survival.

Furthermore, drug-loaded NCs were released at lower pH. Mondal et al. [140] utilized an easy synthetic method with a two-step hydrothermal and wet chemical deposition technique for the synthesis of iron oxide nanoparticles (Fe_3O_4), hydroxyapatite (HAp), and coated hydroxyapatite (Fe_3O_4−HAp) for the treatment of cancer via magnetic hyperthermia approach. First, a controlled hydrothermal synthesis procedure was employed to synthesize Fe_3O_4 nanoparticles followed by coating with HAp. The cytotoxicity study of synthesized iron oxide, HAp, and Fe_3O_4−HAp nanoparticles was performed with MG-63 osteosarcoma cell lines. The Fe_3O_4−HAp nanoparticles were further studied for in vitro hyperthermia assessment. The promising results encourage the future application of Fe_3O_4−HAp nanomaterials as a nanoheater for magnetic hyperthermia−mediated cancer therapy (Fig. 13.9). Along this line, DOX-loaded degradable MSNs with hyaluronic acid (HA) decoration (DOX-loaded HA-PMSNs) for cancer treatment were synthesized by Palanikumar et al. [141]. The release profile of DOX@MSN/CS-PMAA depicted that the DOX release rate was more dependent on pH in DOX@MSN/CS-PMAA than DOX@MSN, whereas a faster release behavior was observed with decreasing pH from 7.4 to 6.8 and 5.5 in DOX@MSN/CS-PMAA system (Fig. 13.9). This issue is attributed to the effect of electrostatic interaction between DOX and polymer nanoshells.

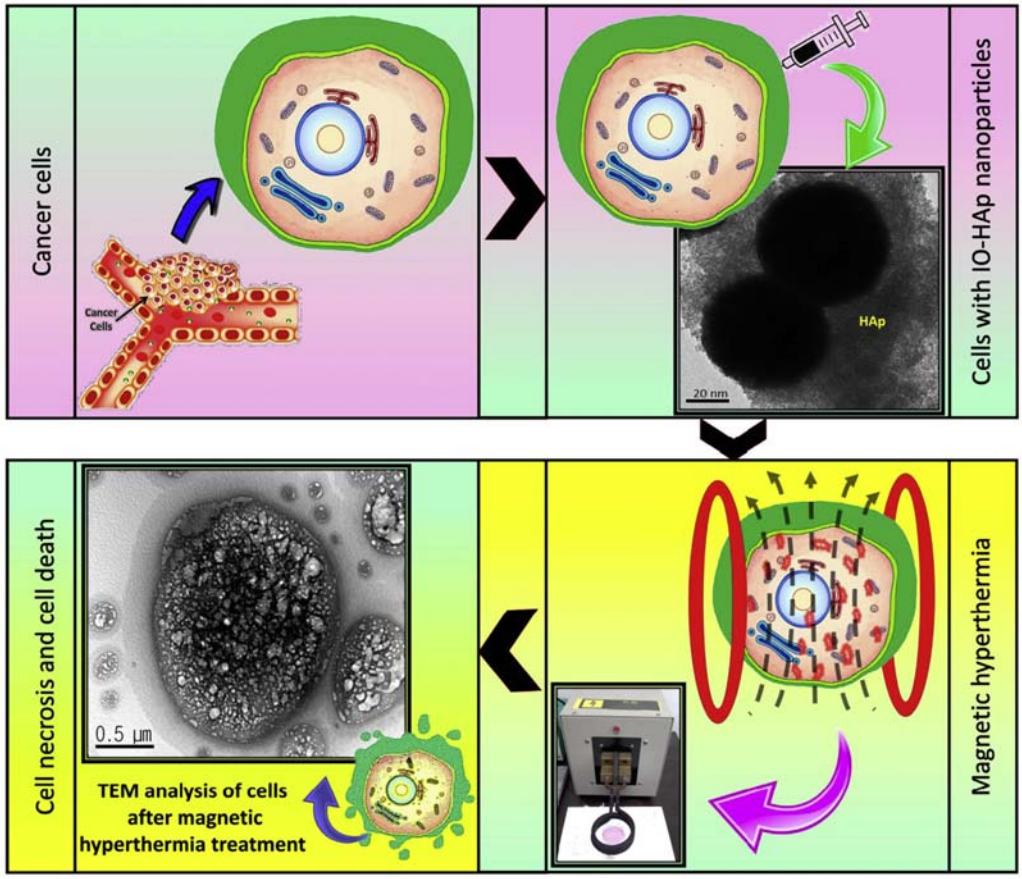

Figure 13.9
Magnetic hydroxyapatite (IO-HAp)—mediated hyperthermia study to treat cancer [140].

Nanoselenium-poly-L-lactic acid (nSe-PLLA) NCs have been prepared to reduce bone cancer cell functions by Stolzoff and Webster [142]. The SeNP—PLLA samples had a greater alkaline phosphatase (ALP) activity than healthy osteoblast tissue. Antioxidant-loaded phosphorylated chitosan nanohydroxyapatite (HAp/PCS) and phosphorylated chitosan—nanohydroxyapatite—gingerol (HAP/PCS/G) composite scaffold for bone tissue engineering was developed by Sumathra et al. to accelerate cell proliferation [143]. The investigation showed that HAP/PCS/G composite scaffold had good properties as large pore size, biocompatibility, and cytotoxicity and could be used as an osteoconductive scaffold. In another study, Wu et al. prepared JQ1 (a bromodomain inhibitor)-loaded n-HAp with and without Medronate (BP) as an amino acid protein [144]. According to this study, the OS cell was selected by loaded n-HA with BP. The positive effects of this synergy are evidenced by the consistently favorable effect achieved by HAp/BP/JQ1, not

only reduced OS cell migration and viability of differentiated OS cells more than any other HAp composition, but also selectively necrotized OS cells, similar to HAp/JQ1 and HAp/BP.

Silica nanostructures (n-SiO_2) as nanocarriers, due to advantages, such as biocompatible, highly porous, easy-to-control fabrication, cost-effective, and easy to modify for functionalization nature, have been widely used in drug delivery [145−148]. MSNs were first synthesized by Kresge et al. [149]. The study reported that the fabrication of interaction of silanol group of mesoporous n-SiO_2 (MSNs) with cellular membranes could cause toxicity [149]. Therefore, surface modification of the MSNs with a polymer shell is highly required to utilize them for potential anticancer as well as other biomedical applications [150].

4. Conclusion

This chapter explains NCs with different nanofillers and their great potential as a single platform with multifunctional capabilities for slow and controlled drug delivery emerging as an attractive approach as compared with the traditional treatment containing chemotherapy drugs, radiation, and surgical excision; NCs functionalized with a targeting agent present a novel therapeutic approach. The entrapment procedure of chemotherapy drugs into the NCs has resulted in more significant drug loading and slower drug release properties. However, despite many remarkable studies, some critical questions need to be answered toward clinical applications. Therefore, more data are required about the appropriate shape and size nanofiller currently doped into the polymers. Subsequently, more attempts should be made to improve nanofillers' synthesis and properties for successfully transporting chemo drugs to purposed targets. Besides, extra in vitro and in vivo experiment for enhancing drug delivery from these nanocarriers is demanded.

Furthermore, several types of PNCs cannot be scaled up due to the high-cost process. In this regard, nanocarriers based on PNCs should be fabricated at low cost and fast. The next major challenge encountered in PNC for drug delivery is their biocompatibility and acceptability since synthetic materials with body cells in vivo experiments are different from in vitro tests and in biological media. Besides, fundamental challenges in PNC systems are stability, solubility, permeability, and sustained release.

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CHAPTER 14

Bionanomaterials for diagnosis and therapy of SARS-CoV-2

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1. Introduction

1.1 Overview

In December 2019, outbreak of a disease with severe respiratory syndrome and simultaneous death was seen in the Wuhan province of China. It was termed as n-CoV-2 or COVID-19 [1,2]. It is a highly contagious disease with a large basic reproducible value of ($R_0 = 3.77$), which is much more contagious than Ebola, flu, and earlier found corona virus–related diseases [3]. This disease spreads dangerously breaking the barriers of province or country. It is transmitted worldwide within months. The World Health Organization (WHO) declared it as a Public Health Emergency of International Concern (PHEIC) on February 16, 2020, and alerted every country, but by then, it had spread worldwide and aroused a global pandemic [1,4]. Every country, rich or poor, small or large, tried to take drastic measures to prevent it, but the disease came as a massive blow to our global health and economy, killing 4.29 million lives to date.

Nations worldwide hurried to prevent the spread of this disease through severe lockdowns, thorough travel bans, and rigorous social distancing [5]. The WHO gave the guidelines to wear a mask, frequently wash hands with soap, use sanitizer, and maintain social distancing of at least 6 feet apart in public. Every nation engaged their scientists to urgently discover the genome sequences of the new virus, SARS-CoV-2 or COVID-19, and to elucidate proper medicine after diagnosis of the severe disease [6]. Nations worldwide have also laid key focus on rapid and precise detection of the pathogen in infected patients. Doctors and healthcare workers worldwide are engaged day and night to save the lives of infected patients and have tried to discover a proper line of action to provide a stable healthcare system for this pandemic. Finally, key resources worldwide have been focused on the discovery of a proper vaccine, the definite curative measure to wipe out the pandemic. The discovery of a vaccine for SARS-CoV-2 and its proper

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implementation through rigorous human trials is a long-term phenomenon. All scientists, engineers, and doctors across the globe have been actively engaged on this target, and we have made immense progress. Along with the successful discovery of the vaccine, we also have to live our life taking preventive measures, and nanoscience can play a key role in both these aspects. This is because viruses are living nanomaterials.

1.2 Genome study and nature of n-CoV-2 virus

When an epidemic starts, the first task of scientists is to discover the genome structure of the pathogen. Wu et al. have been the first to point out the genome sequence of the new pathogen for this deadly COVID-19 pandemic [7]. Phylogenetic analysis of the viral genome depicts that the virus was closely related to a SARS-like coronavirus or Genus *Betacoronavirus*, subgenus *sarbecoronavirus*. These *Betacoronaviruses* were detected earlier and found in China. Wu. et al. have analyzed the new 29,903 nucleotides viral genome for genome sequences as well as its termini [7]. They have determined the sequence with the aid of the fundamental process of reverse transcription polymerase chain reaction (PCR) and have confirmed it by the 5′/3′ rapid amplification of cDNA ends (RACE). The virus strain was named as WH-Human 1 coronavirus (WHCV) or as "2019-nCoV." The whole-genome sequence (299,031) has been assigned as Gen Bank accession no. Mn908947. Remapping the RNA sequencing data to the complete genome coverage of the new pathogen read at 123,613 assemblies, exhibiting a protruding 99.99% genome coverage at a mean depth of 6.04 × (range: 0.01−78.84×). The viral load of bronchoalveolar lavage fluid cell (BALF) sample from the patient has been estimated by quantitative PCR (QPCR) to be 3.95×10^8 copies/mL.

The SARS-CoV-2 virus is spherical and approximately 62−140 nm in size [8−10]. It contains a single-stranded RNA genome of ∼30,000 nucleotides encoding 27 proteins. Four structural proteins, the spike surface glycoprotein (S), a small envelope protein (E), matrix protein (M), nucleocapsid protein (N), and an RNA-dependent RNA polymerase make up the SARS-CoV-2 virion structure. Some sequence diversity of the virus has also been reported [11]. Fig. 14.1 shows a schematic and transmission electron microscope (TEM) image of SARS-CoV-2 [12]. SARS-CoV-2 are zonotopic pathogens and have infected humans via interspecies transmission. These viruses are believed to jump from their natural hosts (bats) to an intermediate adaptive animal before human transmission. The SARS-CoV-2 pathogen interacts with human angiotensin-converting enzyme 2 (ACE2) via their S protein [13−15]. Wrapp et al. have studied the structural conformations of the SARS-CoV-2 S protein via cryo-TEM and subsequent ab initio three-dimensional (3D) reconstructions of the micrographs [16]. They have shown that this virus exhibits a stochastic receptor-binding movement mediated through its spike proteins, similar to other *Betacoronaviruses*. The receptor-binding domain (RBD) of the S1 subunit of the spike protein undergoes hinge-like transformations that expose (i.e., up

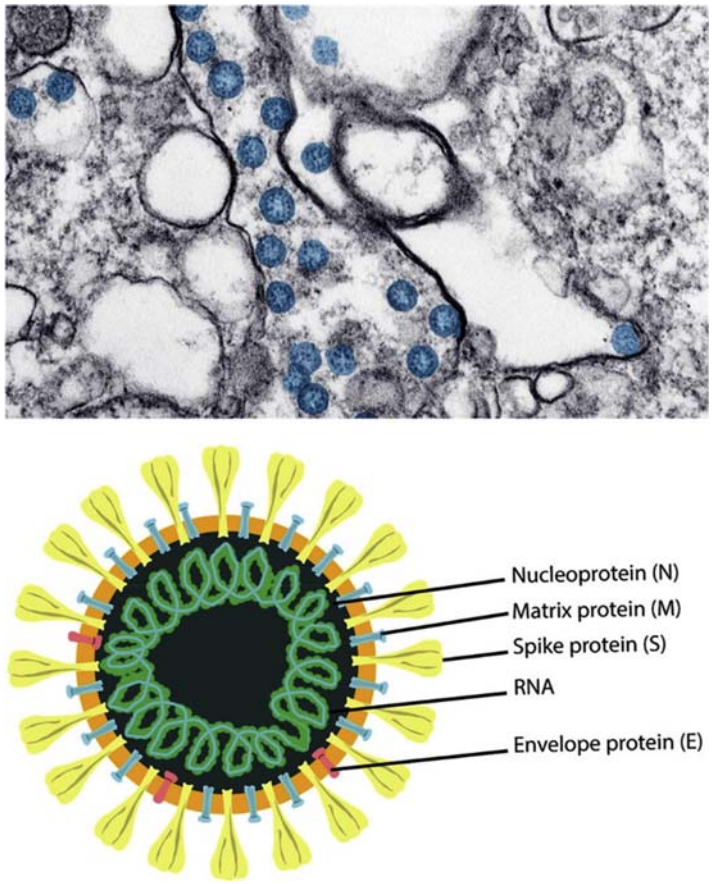

Figure 14.1
SARS-CoV-2 morphology. Transmission electron microscope image of SARS-CoV-2 spherical viral particles in a cell. The virus is colorized in blue (adapted from the US Centers for Disease Control). Representation of the viral structure is illustrated with its structural viral proteins. *Reproduced with permission from B. Udugama, P. Kadhiresan, H. Kozlowski, A. Malekjahani, M. Osborne, V. Li, H. Chen, S. Mubareka, J. Gubbay, W. Chan, Diagnosing COVID-19: the disease and tools for detection. ACS Nano 14 (2020) 3822−3835.*

conformation) or hide (i.e., down conformation) the determinants of receptor binding in the presence of a host cell membrane. Binding to the host cell receptor results in destabilizing the prefusion trimer, detachment of the S1 subunit, and a subsequent stable conformation of the spike protein through the S2 subunit. The SARS-CoV-2 S protein shows a high binding affinity to human ACE2 receptor. Wrapp et al. have explained from the structural evidences of the 2019-nCoV-S protein that it binds to ACE2 with higher affinity than SARS-CoV S ectodomain. ACE2 has bound to the n-CoV S ectodomain with −15 nM affinity, which is 10- to 20-fold greater than ACE2 binding to SARS-CoV S.

This makes SARS-CoV-2 more transmissible and deadlier than other *Betacoronaviruses*, inducing the global pandemic. The RBD of this virus is small (∼21 kDa), making nanotechnology strategies more attractive in our fight against the virus. In his 2020 editorial, Chan has recommended application of novel nanomaterials for rapid point-of-care tests, diagnostics for surveillance and monitoring, therapeutics, and vaccine development for COVID-19 [17].

1.3 Objective and significance of the chapter

In this chapter, we review the current state-of-the-art in novel bionanomaterials-based technologies used to combat COVID-19. We highlight the role of bionanoparticles (NPs) in the destruction of n-CoV-2. We first capture the key scientific discoveries made in the structural analysis of this new RNA virus to better understand the pathogen for designing novel combat strategies. We summarize the current technologies and potential of NPs as next-generation smart disinfectants against this pathogen. The key progresses made in the detection, therapy, and vaccination of SARS-CoV-2 with nanotechnology are highlighted as separate sections in this chapter. We conclude with a perspective on the most recent technological updates and biosafety measures for COVID-19. We also identify future bionanomaterial-based approaches and advances to combat this disease. We have aimed to provide key technological knowledge in NP-based disinfection, diagnostics, medicine, and vaccine against SARS-CoV-2 through this chapter to further facilitate emergent technologies and invention in this field. Nanoscience or nanobiotechnology approaches have been at the forefront in preparing sanitizer, mask materials, and effective and rapid methods to determine the pathogen or corresponding antibody, drugs, and biosensors for this new pathogen [10,18]. Detection, disinfection, drug delivery, and vaccinations are the essence to combat this pandemic, and scientists are on their way to develop nano-based materials for the detection and treatment of COVID-19.

2. Disinfection

The NPs are suitable for the destruction of n-CoV-2 pathogens because of their broad range of antiviral activity. Chemical disinfectants are required in high concentrations and large dosages that are harmful for both the environment and patients. In comparison, NPs are effective at small dosages and can reliably disinfect large areas from the pathogen [19,20]. They can enhance the effectiveness of personal protective equipment, surface cleaning, and filtration of airborne pathogens [21]. Coronaviruses have been known to have a capacity of persisting on surfaces [22]. To this end, personal protection equipment provides an essential line of defense against the widespread dissemination of SARS-CoV-2, especially for our healthcare personnel and immunocompromised population and in indoor settings. These equipment are generally used as disposable

short-term protection, as they lack an antimicrobial or antiviral coating. Our indoor air filters also suffer similar limitations. To this end, silver nanocluster/silica composite coating deposited via a patented cosputtering technique on facial masks has shown groundbreaking effect against n-CoV-2 pathogen [23]. These NP-enabled disinfection technologies can provide us with reliable protection against viral and microbial pathogens in nearby and indoor settings [24]. On the other hand, NanoTech Surface, Italy, has invented a durable and self-sterilizing titanium dioxide and silver ion formula for disinfecting the surfaces [25]. FN Nanotech, United States, has produced novel photocatalytic coatings based on titanium dioxide NPs that can destroy the organic compounds on surfaces and on exposure to light can damage the virus membranes [19]. Furthermore, nanomaterial disinfectants have the unique ability to generate reactive oxygen species (ROS). They possess size-controlled photodynamic and photothermal capabilities that cannot be achieved with bulk chemical disinfectants. However, it should be noted that biodegradable or polymeric nanomaterials are more environmentally friendly and safer for long-term use as disinfectant technology.

3. Detection and diagnostics

Fast and real-time detection of this new pathogen is an urgent requirement for us, as there are limited treatment options against SARS-CoV-2. Real-time reverse transcription−polymerase chain reaction (RT-PCR) and quantitative RT-PCR (RT-qPCR) are the standard procedures for detection and diagnosis of COVID-19, and they have been recommended by the CDC, the WHO, and the EU [26]. RT-PCR tests have been widely used in this pandemic to diagnose COVID-19 cases using respiratory samples from patients such as nasopharyngeal or oropharyngeal swabs, sputum, lower respiratory tract aspirates, bronchoalveolar lavage, and nasopharyngeal wash/aspirate or nasal aspirate. This test is used to assess the nucleic acids from SARS-CoV-2 and is used for both individual tests and tests of pooled samples from individuals. An outline is given here for the RT-PCR analysis of mRNA (Table 14.1).

However, testing is limited to certified laboratories with proper equipment capability, and the tests require six to 7 hours. These are some crucial impediments to the high volume of tests required during the pandemic. Therefore, there has been a major research thrust for alternative rapid diagnostic technologies and sensors to detect the SARS-CoV-2 pathogen from infected individuals (Table 14.2).

Nanotechnology-based sensors have played a key role in these new and rapid detection technologies for COVID-19 [27−29]. Biosensors designed from NPs such as carbon nanotubes, quantum dots, gold, silver, and metal oxides have been known to be highly effective for the detection of other viral pathogens (e.g., human immune deficiency virus (HIV), H5N1 influenza virus, and Ebola). The NPs have high surface-to-volume ratios,

Table 14.1: Summary of preparation and the testing process of RT-PCR.

Items	Corresponding sample handling and analysis steps	
Upon receipt of r-RT-PCR panel reagent	Protocol A • Resuspend primer/probe • Mix aliquot • Store at −20 °C (A) • Oligonucleotide primers used	Protocol B • Resuspend and aliquot n-CoV-polymerase chain • Store at −70 °C (B) • Selected from regions of the n-CoV-2 virus nucleocapsid gene
Upon obtaining sample	1. Extract sample RNA and HSC RNA 2. Prepare master mix (15 µL) 3. Prepare r-RT-PCR plate (5 µL RNA) 4. Run assay on ABI7500FAST Dx 5. Analyze data 6. ***Report results***	

Table 14.2: Key nanotechnology-based COVID-19 diagnostics with potential for point-of-care use are summarized in this section.

No.	Type of emergent diagnostic technology reported	Type of journal article	Type of NPs and biomaterials reported	Reference no. and Journal name
1	Analytical approaches	Review	Au, carbon nanotubes, superparamagnetic iron oxide, Ag, quantum dots, metal−organic frameworks, graphite, and immobilized proteins and DNA conjugates	[27], Analytical Methods
2	Biosensors	Review	Au, carbon nanotubes, graphene oxide, silica, metal oxide, aluminum, copper, magnetic NPs, and quantum dots	[28], TrAC Trends in Analytical Chemistry
3	• RT with loop-mediated isothermal amplification coupled with NP-based biosensors • Electrochemical sensors • Chiral biosensors	Review	Quantum dots, Au, and graphene	[29], Nano Express
4	Chemiluminescent homogeneous biosensor	Research article	Phthalocyanine-dyed polystyrene and quantum dot-doped polystyrene	[30], Analytical Chemistry
5	Colorimetric assay for naked eye detection	Research article	Au NPs coated with antisense oligonucleotides	[31], ACS Nano

Table 14.2: Key nanotechnology-based COVID-19 diagnostics with potential for point-of-care use are summarized in this section.—cont'd

No.	Type of emergent diagnostic technology reported	Type of journal article	Type of NPs and biomaterials reported	Reference no. and Journal name
6	Dual-functional plasmonic photothermal biosensors	Research article	Au nanoislands	[32], ACS Nano
7	Plasmonic device for femtomolar detection with standard bioassays	Research article	Au nanorod on bovine serum albumin scaffold	[33], Nature Biomedical Engineering
8	Field-effect transistor-based biosensor	Research article	Graphene	[34], ACS Nano
9	Lateral flow immunoassay	Research article	Lanthanide-doped polystyrene	[35], Analytical Chemistry
10	• Lateral flow assay • Enzyme-linked immunosorbent assay (ELISA) • Colloidal gold immuno-chromatographic assay • Chemiluminescent immunoassay	Review	Au and Au nanorods	[36], Biomedicine and Pharmacotherapy
11	• RT with loop-mediated isothermal amplification • Lateral flow assay • CRISPR based SHERLOCK • ELISA • Proximity ligation assay	Review	CRISPR, enzymes, and DNA-tagged aptamers or antibodies	[37], ACS Sensors
12	Antibody test coupled with paper-based ELISA	Research article	Rabbit antihuman immunoglobulin conjugated with horseradish peroxidase	[38], Analyst
13	CRISPR-Cas13a with cellular phone-based fluorescence plate reader for the detection of SARS-CoV-2 RNA	Research article	CRISPR-Cas13a	[39], Cell
14	• Biosensor • Field-effect transistor • Dual-functional photothermal sensor • CRISPR-Cas lateral flow assay • CRISPR-Cas fluorescence assay	Review	Quantum dots, Au, Ag, metal oxides, graphene, Au nanoislands, and CRISPR-Cas13	[40], Nature Materials

tunable optoelectronic properties, and larger active surfaces for binding. Therefore, the NP-based biosensors offer high specificity to the target biomolecule, rapid detection, and the capability to determine low concentrations of the target analyte as compared with the traditional techniques. For example, a phthalocyanine dye and quantum dot-doped polystyrene NP system has been developed as an enhanced chemiluminescent biosensor for detecting target analytes in low-volume biological samples [30]. This fluorescence resonance energy transfer-based biosensing system overcomes the common limitations of immunoassays such as the extensive washing steps required to prevent nonspecific binding of the target. These NP-based strategies have been applied toward designing faster, easily accessible, and cost-effective technologies for the detection of the new viral pathogen, SARS-CoV-2 to combat this pandemic.

Various NP-based sensors and kits are ready for SARS-CoV-2 tagging and simultaneous detections. Fig. 14.2 provides an overview of these sensors [24]. However, to improve the reproducibility and to eliminate some false-positive results, the researchers at Maryland University have developed a novel colorimetric determination system that is based on gold NPs capped with thiol-modified antisense oligonucleotides. These antisense oligomers are specific to N-genes of SARS-CoV-2, and this new AuNP-based assay can diagnose positive COVID-19 cases within 10 min from the separated RNA samples [31]. One of the challenges is the detection of low viral loads of SARS-CoV-2. This limitation has been addressed by a research team at ETH Zurich, Switzerland. They have invented a dual functional plasmonic biosensor chip containing two-dimensional Au nanoislands that combine a plasmonic photothermal effect and localized surface plasmon resonance sensing transduction to provide a remarkable method of detecting n-Cov-2 viruses up to concentrations as low as 0.22 pM [32]. Luan et al. have designed novel plasmonic nanoprobe addition units for standard bioassays to enhance the signal-to-noise ratio of these traditional assays for the detection of low sample volumes of biomarkers [33]. These multifunctional NP-based probes consist of a bovine serum albumin platform with fluorophores, gold nanorods as the plasmonic agent, and biotin as the component for the detection of biomarkers with high specificity and sensitivity. This novel NP add-on for common bioassays can bring breakthrough advancements in the detection of low volumes of SARS-CoV-2.

Another rapid and accurate detection method for SARS-CoV-2 developed by Seo et al. is a field-effect transistor (FET)—based biosensing device. The sensor consists of SARS-CoV-2 spike protein antibodies immobilized on a graphene FET via the 1-pyrene butyric acid *N*-hydroxysuccinimide ester (PBASE) linker to detect SARS-CoV-2 spike protein antigen in clinical samples even at low concentrations. The device can detect spike proteins as low as 1.31×10^{-3} pM in clinical transport medium and shows no interference from MERS-CoV antigen. This new diagnostic device is unique in its specificity and sensitivity to the SARS-CoV-2 pathogen [34]. Another rapid and precise diagnostic method suitable

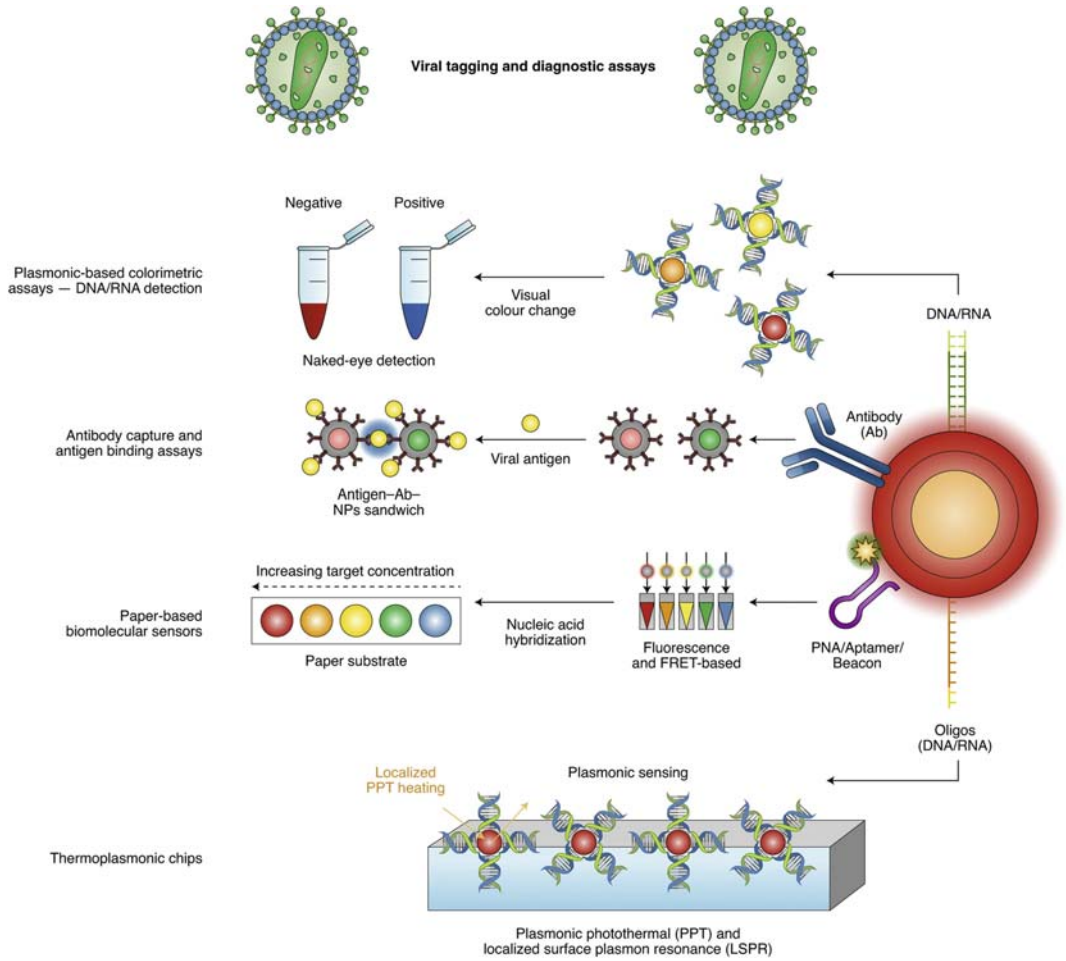

Figure 14.2

Nanotechnology-based sensors for SARS-CoV-2 detection, involved in the development of platforms for viral tagging and nanodiagnostic assays. *Reproduced with permission from S. Talebian, G.G. Wallace, A. Schroeder, F. Stellacci, J. Conde, Nanotechnology-based disinfectants and sensors for SARS-CoV-2. Nat. Nanotechnol. 15 (8) (2020) 618–621.*

for large sample loads common in hospital settings is a novel lanthanide-doped polystyrene NP-based lateral flow immunoassay invented by Chen et al. [35]. It is an analytical procedure that uses lanthanide-doped NPs synthesized via miniemulsion polymerization from tris(1,3-diphenyl-1,3-propane dionato) (1,10-phenanthroline) europium-(III), styrene, acrylic acid, 2,2'azobis (isobutyronitrile), and cetyltrimethylammonium [30]. The lanthanum-doped NPs are dispersed in water (5% w/v) and stored at 4 °C before surface functionalization with mouse antihuman IgG antibody (M-H IgG) and rabbit IgG (R IgG). The lateral flow immunoassay for SARS-CoV-2 is

fabricated with these NPs via slight modification of a previously reported procedure [30]. The serum samples are diluted with assay buffer (1:1000), and 100/μL of the diluted sample is added to the sample well of the lateral flow immunoassay strip for analytical assessment. When the test solution migrates from the sample pad to the absorbent pad, the functionalized lanthanide-doped polystyrene NPs are accumulated at the test and control lines as shown in Fig. 14.3. After settling for 10 min, the test strip is uploaded to the

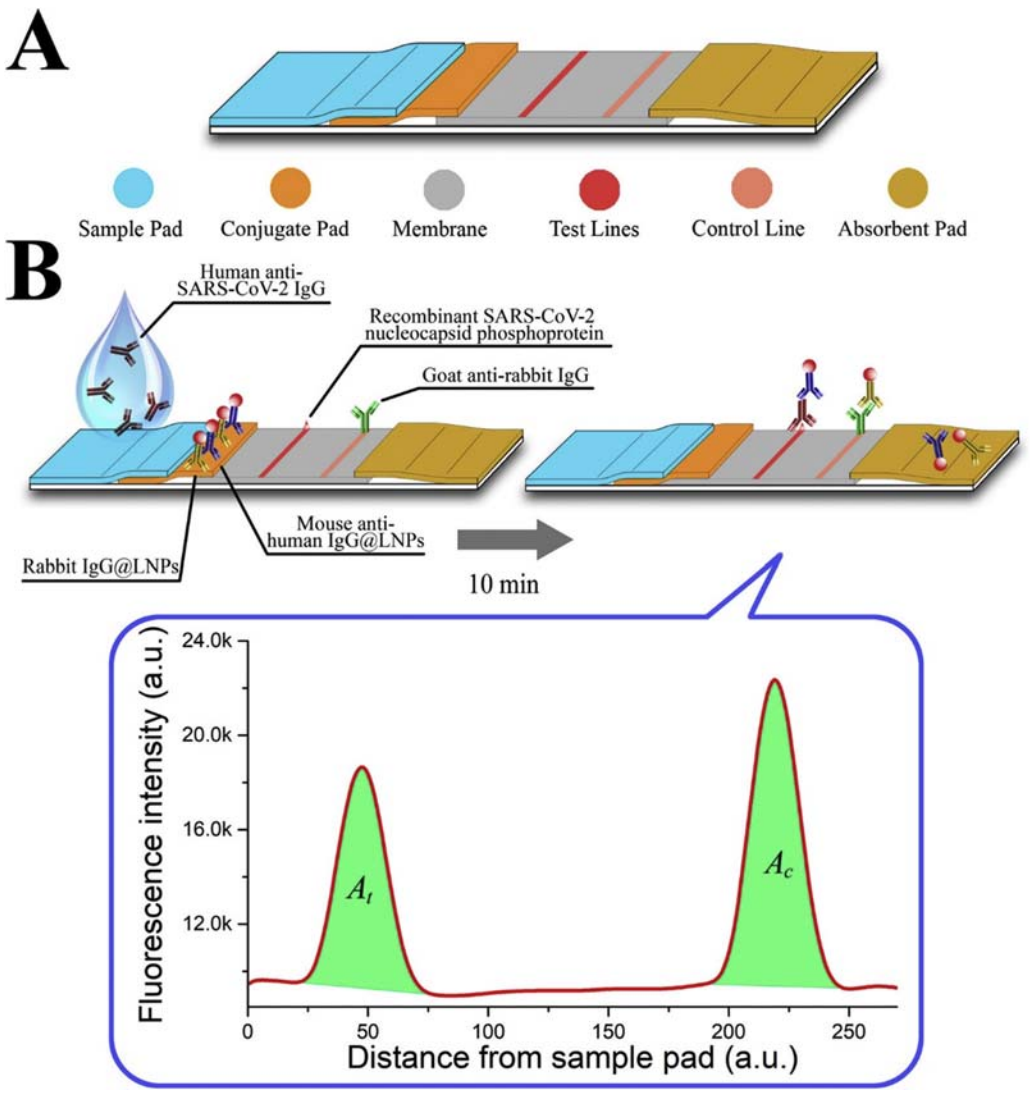

Figure 14.3

Design and fabrication of the developed assay. (a) Lateral flow test strip. (b) Assay. *Reproduced with permission from Z.H. Chen, Z.G. Zhang, X.M. Zhai, Y.Y. Li, L. Lin, H. Zhao, L. Bian, P. Li, L. Yu, Y.S. Wu, G.F. Lin, Rapid and sensitive detection of anti-SARS-CoV-2 IgG, using lanthanide-doped nanoparticles-based lateral flow immunoassay. Anal. Chem. 92(10) (2020) 7226–7231.*

portable fluorescence reader for the measurement of fluorescence at an excitation wavelength of 365 nm and an emission wavelength of 615 nm with a delay time of 20 μs. The results are quantified from the areas of the fluorescence peaks of the test line, *At*, and the control line, *Ac*. The *At:Ac* ratio (R) denotes the anti-SARS-CoV-2 IgG concentration in the serum. The optimum time for maximum fluorescence is 10 min for this lateral flow assay. The reproducibility or coefficient of variation of this immunoassay is 11.5%−14.63% (i.e., <15%). This rapid and sensitive method is comparable with RT-PCR and may be more accurate than RT-PCR for suspected SARS-CoV-2 patients [6,26].

Currently, the RT-PCR-based technology serves as a gold standard for the detection of SARS-CoV-2, but the method requires expert personnel, advanced instrumentation, and 4-6 h to generate results. Antibody-based testing is another key approach used in COVID-19 detection. The antibody tests are based on the detection of antibodies or immunoglobulins, i.e., Y-shaped proteins produced by the patients' immune response as a defense against the SARS-CoV-2 virus. Several emerging points of care technologies for SARS-CoV-2 are using antibody-based tests coupled with immunoassays such as lateral flow, time-resolved fluorescence, or plasmonic nanoparticles [36,37]. For example, a paper-based ELISA with specific antigens has recently been designed for detection of SARS-CoV-2 antibody with colorimetric readout based on 3,3′,5,5′-tetramethylbenzidine-horseradish peroxidase reaction [38]. However, detectable limits of antibodies are not developed early in the disease. Patients who have recovered from SARS-CoV-2 also possess these antibodies, which defend them against further infection. These are some of the current issues limiting the efficacy of antibody-based detection. A recent model has highlighted the significance of frequent testing and fast turnaround of results over sensitivity of tests in combating the transmission of this virus [39].

Therefore, new clustered regularly interspaced short palindromic repeats (CRISPR)−based strategies have emerged for point-of-care diagnosis of COVID-19 [40]. CRISPR-Cas originally developed as an approach to minimize phage transmission in bacteria has now provided us with a key resource for viral RNA detection with a rapid turnaround of 1 h. Cas13 enzyme from the bacterial immune system can directly bind to single-stranded RNA. This Cas13 protein is conjugated with programmed CRISPR RNA to form a nuclease-inactive ribonucleoprotein complex, which on binding with its complementary RNA sequence can cleave any surrounding single-strand RNAs. The binding and cleavage of Cas13 can be rapidly detected via a single-strand RNA-fluorophore quencher pair. A preamplification of the target RNA is used to enhance the sensitivity of the CRISPR-Cas13 approach for the detection of SARS-CoV-2 in the SHERLOCK protocol. The CRISPR-Cas13-based DETECTR approach can avoid the conversion of amplified DNA back to RNA and has also been approved by the FDA. Both these CRISPR approaches are attractive as the point-of-care tests, as they can be read via lateral flow

paper assays. Recently, Fozouni et al. have reported a CRISPR-Cas13a-based direct and portable assay that does not require preamplification of the SARS-CoV-2 genome and can provide the detection results within 5 min of measurement via a mobile phone app [39]. This assay can detect up to ∼100 copies/μL of SARS-CoV-2 RNA in 0.5 h, whereas the other two FDA-approved CRISPR methods require 1 h for detection. Thus, the CRISPR strategy has been a novel breakthrough for COVID-19 diagnostics with the potential for being developed into COVID medications.

4. Medicine

A vaccine will help end this deadly COVID-19 pandemic. However, until its discovery and availability to the public, doctors all over the world are making tremendous efforts to treat the enormous numbers of COVID-19 patients and to cure them. To this end, there is constant research for medicine against this deadly pathogen. Hydroxychloroquine, the antibiotic azithromycin, anti-HIV combined drug lopinavir-ritonavir, antiinflammatory antibody, tocilizumab, antiviral drug remdesivir, a combination of remdesivir and baricitinib, and convalescent plasmas from cured patients have been used as a treatment for this disease [41–44]. The use of one of these drugs considered suitable for the respective patient along with oxygen support have been applied as the treatment protocol for COVID-19 by doctors all over the world. Nanotechnology can assist in galvanizing the potency and efficiency of COVID-19 drugs as NPs can be targeted to the diseased cells, have a longer circulation time in vivo, and can accumulate in the macrophages [45,46]. Nanomedicines can also be administered via inhalation or intravenous injection. Therefore, nanomedicines can bring breakthrough advancements in efficacy against SARS-CoV-2. They offer key advantages in drug availability and drug activity compared with their bulk counterparts, which can facilitate enhanced lifesaving capacity against this pathogen. It is now established that dexamethasone (6 mg/day), administered orally or through intravenous injection for 10 days, improves the condition of fatal patients by 35%. This has been discovered through one of the world's largest randomized trials on COVID-19 patients. This drug also reduces the hospitalization time and chances of fatality in nonventilated patients. Lammers et al. have proposed that a new nanoformulation consisting of dexamethasone liposomal NPs will bring further groundbreaking improvements in the efficiency of this drug [41]. Liposomal dexamethasone has been a successful drug for several diseases including myeloma, multiple sclerosis, liver fibrosis, and rheumatoid arthritis. Reformulation of this drug in the nanoform has been shown to outperform the dexamethasone itself. However, nanoformulations are costlier and achieving economic viability as well as timely regulatory approval are some of the impediments of nanomedicine [47–51]. On the other hand, the fact that corticosteroids such as dexamethasone are well-known antiinflammatory drugs to prevent inflammation and propagation of phagocytic cells in the lungs is a key advantage in terms of cost and

regulatory approval of the nanoformulation. Cortisol is both cheap and an easily available standard drug [47]. A combination of cortisol and the antiviral drug is used in some cases by physicians to treat SARS-CoV-2 infections. At present, scientists also suggest that nitrous oxide inhalation is a supportive avenue for COVID-19 patients [52]. Inhaled nitrous oxide is approved by the US FDA for the treatment of patients requiring long-term oxygen therapy and pulmonary hypertension in newborns. The equipment to facilitate nitrous oxide inhalation in patients is inexpensive, relatively noninvasive as compared with the mechanical ventilation units, and can be arranged at home. Therefore, the therapy is significantly attractive as a cost-effective and efficient treatment option for SARS-CoV-2-infected patients. This treatment has recently shown tremendous results for a COVID-19 patient with pulmonary arterial hypertension. Another novel approach for COVID-19 medicine has focused on the infected host cells instead of targeting the pathogen [53]. This innovative technology is based on a new nanosponge formulation synthesized from membranes of human cells (e.g., human lung epithelial cells and macrophages), which are typically targeted by SARS-CoV-2. The nanosponge is surface-functionalized with the same protein receptors used by SARS-CoV-2 for entry to human cells. These nanosponges can successfully neutralize the n-CoV-2 pathogen and incapacitate it from attacking the host cells. Thus, there is an ongoing global search through innovation, experimentation, and trial and error for the invention of supportive medicines for COVID-19 infections [54].

5. Vaccine development

It is suggested that SARS-CoV-2 S shares 98% sequence identity with the S protein from the bat coronavirus RaTG13 and it is evident that understanding the nanoscale and atomic-level structure of 2019-nCoV spike proteins will help in the development of a vaccine. Daniel Wrapp et al. have determined the structure of the 2019-n CoV spike in the prefusion conformation. They can provide a 3.5-angstrom resolution structure of 2019-nCoV S protein trimer in the perfusion conformation via cryo-TEM [16]. All these atomic-level structural information will support precision vaccine invention and the discovery of the correct antiviral therapeutics. Scientists throughout the world are engaged in vaccine preparation. It is now in focus that the S-protein is the most reliable target for the development of the COVID-19 vaccine [55]. This pandemic has galvanized innovations and next-generation technologies for accelerated vaccine development as it is a new target virus. North America, Europe, China, Asia, and Australia have led the endeavors in vaccine development with active engagement from public and private sector firms, multinational companies, as well as academia. The Coalition for Epidemic Preparedness Innovations (CEPI) has created an R&D database and vaccine development landscape to support and expedite the invention of a vaccine against this deadly disease. More than 200 vaccines are in the line of action to prove their efficacy. mRNA and DNA-based vaccines offer the advantage of an enhanced level of engineering of the antigen and can be

developed faster. Viral vectors are another attractive platform for vaccine candidates, as they provide high stability and strong immune response. Vaccines based on recombinant proteins effective for other viral diseases can make use of the already existing large-scale production process. We have mentioned at least eight of them, which have begun their human trial or comprehensive efficacy trial [56,57].

- Pfizer-BioNTech COVID-19 vaccine by Pfizer Inc., United States, that has been approved for emergency use for prevention of COVID-19 in individuals of age 16 and above
- mRNA-1273 vaccine by Moderna (Cambridge, Massachusetts, United States)
- Oxford University-AstraZeneca and Covishield vaccine are on the third human trial. They started their human trial on April 16, 2020
- ENSEMBLE, Johnson & Johnson's single-dose COVID-19 vaccine has recently completed its Phase 3 trial over multiple countries
- COVAXINTM by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR), India
- Altimmune's intranasal coronavirus vaccine (Gaithersburg, Maryland, United States)
- INO-4800 by INOVIO Pharmaceuticals, United States
- Avian coronavirus infectious bronchitis virus (IBV) vaccine by MIGAL (Israel)

Biohybrid NPs play a key role in multiple aspects of COVID-19 vaccine development. They can help in vaccine design, delivery, and administration [58,59]. Nanovaccines essentially apply NPs as carriers or adjuvants for the biological components of the vaccine. For example, the NPs can act as a stabilizer for the antigen during the administration process and can enable the synthesis of multivalent antigens [10]. They can serve as a platform for targeted delivery of the antigen to boost up the patient's response. An mRNA vaccine developed by ModernaTX Inc. is among the first to be approved for emergency use against COVID-19. The vaccine encodes a prefusion spike glycoprotein of SARS-CoV-2. One of the key components of this vaccine is the liposomal NP used to encapsulate the mRNA for efficient circulation and delivery in vivo. No mRNA or DNA vaccine has been approved so far for any disease, as the delivery of nucleic acid requires a NP platform to restrict its degradation inside the body [60]. The liposomal NPs have now been approved for RNA delivery. In the long run, nanotechnology will be highly beneficial as an immune-mediated approach against the nCoV-2 or COVID-19 pathogen.

6. Perspective

The NPs offer a wide range of transport, biointeraction, optical, magnetic, and electronic properties that are not available in macroscale or molecular materials [9,61]. The surfaces of nanocarriers can be readily functionalized with multiple peptides and biomarkers to both detect and treat the pathogen [13]. These properties can be exploited to advance

novel innovations in target-specific drugs, sensors, rapid point-of-care diagnostics, disinfecting agents, and vaccines against the SARS-CoV-2 pathogen [62,63]. A fundamental understanding of bionanointeractions can be used to uncover the mechanisms of interaction of the SARS-CoV-2 virus for designing reliable medicines and vaccines against the pathogen. Nanoformulations of glucocorticoids have the potential to further boost the efficacy of this antiinflammatory drug against SARS-CoV-2 and can bring breakthrough advancements in the search for supportive medicine for COVID-19 infections. Two mRNA vaccines with liposomal NPs as their delivery agents are among the first approved prophylactic measures against the novel SARS-CoV-2 pathogen [64,65]. The positively charged lipid NP encapsulation prevents disintegration of the mRNA in vivo, enhanced circulation, and efficient delivery.

In addition, NP-based biosensors can assist in the detection and epidemiological surveillance against this pathogen to curb the global pandemic [66]. For example, a biosensor based on oligomer-coated plasmonic Au NPs has been used as a facile point-of-care colorimetric assay to detect SARS-CoV-2 [31]. Recently, lateral flow assays with novel AuNP tracers designed for the detection of immunoglobulins specific to SARS-CoV-2 have shown promising results comparable with those obtained from PCR [67]. Therefore, there is a huge scope to extend the NP-based diagnostics for SARS-CoV-2 beyond AuNPs using quantum dots and carbon-based materials. A key advantage of these technologies will be their point-of-care capability and cost-effectiveness as compared with the RT-PCR and CT scan-based laboratory approaches. Recently, CRISPR-Cas13 has also evolved as an emergent strategy that has galvanized the point-of-care detection of SARS-CoV-2. The SARS-CoV-2 genome is fast evolving through various mutations in different regions of the globe resulting in new variants. Detection of low viral loading present at the early stages of the disease and limiting all cross-reactivity with viral strains other than SARS-CoV-2 also pose two main challenges for scientists. Therefore, innovative solutions will have to be designed to meet the challenge of prompt point of care detection of this RNA virus [40,68]. Jarrom et al. have suggested the significance of an evidence-based approach in designing strategic framework and standards for COVID-19 testing [69]. The use of single-molecule nanopore sequencing used to characterize long-sized DNA or RNA can also serve as an emergent possibility for the diagnosis of SARS-CoV-2 [70].

One of the methods for the transmission of the SARS-CoV-2 virus to humans is through contaminated surfaces or fomites. To this end, the importance of NP-based antiviral coatings has been suggested as a key resource to combat viral transmission. These smart coatings can serve as innovative solutions for improving our PPE against the virus. NPs such as gold, silver, titanium dioxide, zinc oxide, carbon nanotubes, and biohybrid chitosan can provide next-generation smart antiviral surface coatings through their unique mechanisms of interaction with the pathogen including production of reactive oxygen

species, inhibition of enzyme activity, energy transmission, and DNA damage [71]. Global interdisciplinary collaborations between materials scientists, environmental engineers, biomedical engineers, chemists, and nanoscientists will be the key to engineering these novel surface coatings against SARS-CoV-2.

Ruiz-Hitzky et al. have highlighted the emerging patents on NP-based technologies applied to COVID-19 responses [72]. Recently, new strains of the SARS-CoV-2 pathogen have been detected in Europe. New strains of the pathogen with spike aspartic acid−614 to glycine (D614G) substitution have replaced the parent SAR-CoV-2 virus. Research so far indicates that this new D614G variant has increased transmissibility in humans compared with the ancestral strain but has not evolved in pathogenicity [73]. Current vaccines are believed to show the same efficacy against this SARS-CoV-2 variant. As scientists, doctors, and engineers around the globe search for new avenues to fight this pandemic, several mechanistic insights remain unknown about SARS-CoV-2 [74]. Nanotechnology can continue to bridge this gap in knowledge about the pathogen through structural analysis, new diagnostics, therapeutics, and vaccines. For example, biomimetic 3D human lung models can be designed using hydrogels, pluripotent stem cells, and polydopamine via 3D bioprinting. These 3D models can be used instead of human subjects for understanding the preliminary mechanisms of interaction of SARS-CoV-2 with the new biohybrid NP-based therapeutic and detections agents [70]. Ongoing research on this new pathogen and biohybrid nanomaterials to combat the RNA virus will be critical in preventing surge of new cases and saving lives worldwide [75].

At the same time, biosafety should be of key importance. Regulatory guidance for the general public as well as handling, sample preparation, and analysis of this highly transmittable pathogen are regularly provided through CDC and global regulatory agencies. These guidelines are updated based on the most current research findings. SARS-CoV-2 cell culture, separation, and initial analysis of the samples should be conducted in a biosafety level 3 (BSL-3) laboratory with appropriate regulatory approvals. Samples for testing should be handled in a BSL-2 laboratory with a biosafety hood and with BSL-3 precautions including respiratory protection and proper personal protective equipment. Biosafety needs should be continuously assessed, and new experiments on NP−pathogen interactions should be performed with required regulatory approvals for continued global safety [76].

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CHAPTER 15

Drug delivery systems based on nano-herbal medicine

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1. Introduction

From ancient times, herbs, plants, and natural remedies have been applied to treat patients in every possible condition. Alternatives to artificial therapeutic molecules were utilized for their lower side effects of herbal medicines [1,2]. Numerous references have demonstrated that this type of medicine possesses pharmacological action resulting from its particular constituents. Surely, constituents' content changes from branch to branch because of ecological facts and herb collection volume. Phytopharmaceutical sciences have identified the structure and biological processes of many medicinal plant products. Many biologically active extract components such as flavonoids, tannins, and terpenoids have high water solubility but low absorption. They do not cross lipid membranes, have generous molecular sizes, and display low absorption, causing a lack of bioavailability and effectiveness. Some tests have shown that herbal drugs perform well in in vitro assays that cannot be replicated via in vivo experiments.

Many diseases, such as cancer, diabetes, and arthritis, require personal health responsibility to be continually enhanced in every region. Both academia and industry play a vital part in combining physical and chemical data, research techniques, preparation routes of composites, deterioration pathways, and composite applications. Enhanced efficiency and decreased initial material ingredients are realized through an appropriate technique applied to produce the same materials in nanoscale formations, including improved and new properties for required applications. As a result of a greater surface–volume ratio, the nanosurfaces of these materials are composed of many more

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atoms with a conductive surface, allowing enhanced reactivity in various interactions with other substances. The surface-to-volume ratio is contrariwise proportional to the radius of the particles, meaning that smaller particles lead to larger particle surfaces for more active interaction. Improvements in optical, physical, and mechanical properties are important aspects of the transition from bulk to nanosized particles [3–7].

Phytodrugs have been provided as a severe resource of medicines from the far past, and their application has been enhanced by their remedial acting and reduced side effects compared with other drugs. Both developing and developed societies have the reputation of herbal medicines at their cores, both for their natural sourcing and the rarity of their side effects. Rapid-flourish nanotechnology has served as a powerful reinforcement for developing innovative, pioneering herbal medicines. Nutraceuticals are foods and food components providing health impacts outside essential feeding, but numerous nutraceuticals demonstrate insignificant bioavailability. Uses of nanotechnology in drug manufacture have been assumed to dominate the challenges and technological obstacles relevant to the solvability, bioavailability, strength, and delivery of bioactives from the diet. The growing influence of nutraceutical nanotechnology takes away excellent formulas to grant novel and special functional diets as a gadget for prevention and feasibility, even carrying a cure to several noninfectious infections. To date, many investigations have been formally presented with various primary nanoscale approaches in nanotechnology for herbal drug delivery (DD) and nutraceuticals [8–11]. In the case of diseases, various body organs may be affected, and therefore, the need to develop healthy medicines like nano-herbal drugs to target diseases is of utmost priority to modern researchers. Current drug-delivery systems (DDSs), including biological compounds obtained from higher plants and their uses in the nanomedicine field, are described in Fig. 15.1.

This chapter aims to introduce a preface of nanotechnology in herbal drugs for DDSs. It is possible to apply nanotechnology to enhance the supply of herbal medicines with minor water dissolution, to deliver herbal medicine to cells and over narrow epithelial and endothelial barriers, to free powers, to provide two or more medicines, and to see where medicine is delivered by combining herbal drugs with imaging methods [13–15]. Nanotechnology can formulize herbal medicines and various nanostructured herbal formulas, uses, and biological processes.

2. History and development of herbal medicines

Ancient civilizations were the original witnesses for medical management. Consequently, specialists, researchers, and even patients have considered that traditional medicine with a long history could be born from a natural product with therapeutic features. In this older era, the primary long-term medication sources were mineral, plant, and animal products.

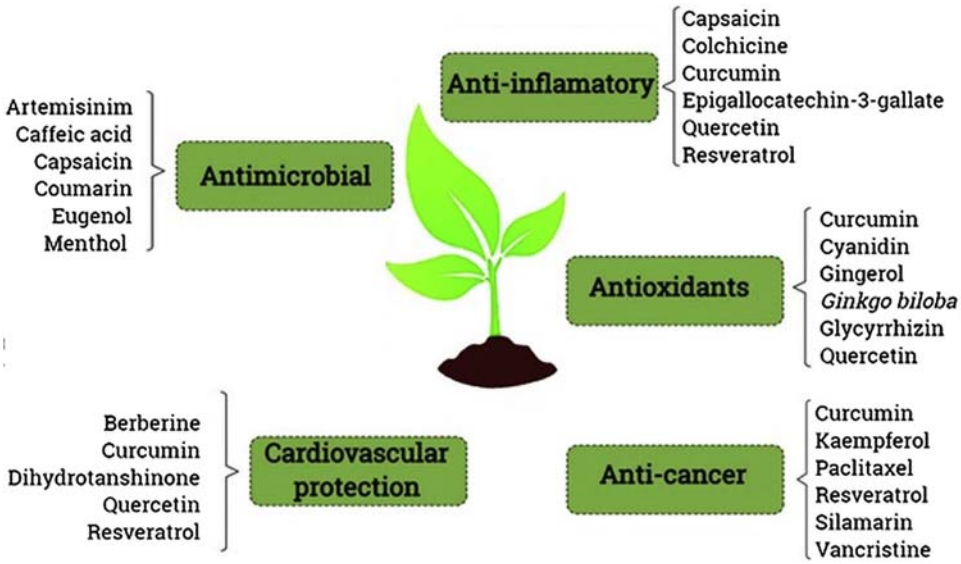

Figure 15.1
An illustration displays many types of natural compounds from medicinal plants in biomedical applications and the treatment of specific ailments [12].

Interestingly, some plants could be used even to treat illnesses and revitalize body systems [16]. It is not simple to determine the precise moment when medicines were used. Medicinal plants are known to have been grown about 60 centuries ago [17]. In addition, records and evidence of medicinal plants exist in India, China, Egypt, Greece, and Central Asia from about 50 centuries ago [18]. Although traditional drugs have not been well explained, their essential healing and harmful medication reactions cannot be disregarded in different places and periods. Since ancient times, several illnesses have been conquered; in practice, approximately 80% of countries worldwide, with different religions, cultures, ethnicities, and geographical regions, have been applying traditional herbs or plants.

The natural source of chemotherapy, in various civilizations, proposed alternative sources of drugs, herbal medicines, and remedies from the initial to final health care procedures. Moreover, today's chemotherapy was derived from these natural medicinal products, referred to as both civilizations and plants belonging to the third millennium BC, that now can respond to 400 different species. Ancient Chinese, Grecian, Egyptian, African, and other civilizations are strong proof of this claim, as seen in these countries' people [19].

According to the World Health Organization (WHO), each plant defines a medicinal plant with its substances for therapeutic purposes or known as precursors of pharmacological science. Roots, stems, rhizomes, flowers, barks, grains, fruits, leaves, seeds, or even the

color of berries and the smell of garlic or union are some of the organoleptic features that are bioactive parts of the plant containing chemicals with medical activities and can be used to control and treat patients.

Expansion of drug prescription needs a practical and comprehensive choice of herbal types, which represent an important element of the production, whether in juice or deficiency. Intangible materials, however, including natural resources, cannot increase to phytomedicine. The technological range of phytomedicine mediation is vital for the outstanding range of products. A common kind of use after the dependability of the purported use, posology (medical components related to dosage), and agricultural document of the herbal substance, for which phytochemical and pharmacogenetic schema will be extended to provide the physical, chemical, and physicochemical specifications of the herb, certifying the concord of examples and the correspondence to instances inquired about during the experimental phase.

Plants, being essential origins of updated drugs, make up 25% of prescriptions for one plant-derived ingredient in the USA at the minimum amount. So in the last few decades, 100 pharmaceutical products have been formalized based on general information. Plant-derived drugs are used in updated medicine using plants as a native cure for drugs. Today, the globe is developing toward medicine-based plants and phytodrug repair and strengthening of sensual systems and damage-violating pathogens without poisonous agents [20]. Herbal extracts are phytochemically anatomized to determine the sample's metabolic category until the next stage. So it must be pharmacologically studied to make sure its activities. Its physical and physicochemical specifications will be characterized, and consequently, it could be identified as the chemical and a pharmacological indication of the plant.

Herbal medicines such as quinine and aspirin, extracted from quinine and willow bark, have treated malaria and fever [18]. In addition, cancer and inflammation have been cured by plants such as colchicine, curcumin (CUR), *Triphala*, pomegranate, guggulsterone, and sariva [21]. Regarding the disadvantages of chemical drugs, many chemical drugs for treatment and prevention of diseases require long-term use, and therefore, toxicity may aggregate over time. In addition, the body's resistance to the drug and compensatory mechanisms are often an issue upon treatment with synthetic chemical drugs. It is also noted that natural products and medicines are significant in the biomedical industry and are experienced and achieved as orderly, regulated systems worldwide. The next drug discoveries improved as they used the substantial available information about traditional medicines' incomparability and modern medicine. For instance, morphine is an active compound produced as a new drug from opium—a natural product that greatly benefits

modern medicine in pain management for cancer patients. Numerous clinical experiences, unique chemical structures, and activities are high-level advantages of new drugs beyond natural medicines.

Some food items and supplements come from natural sources, make it to market, and have lately been accepted by consumers and experts. Due to low stability, absorption, and solubility problems resulting in low therapeutic index of plant actives, researchers seek to minimize the adverse drug reactions (ADRs), improve therapeutic efficacy, and eventually improve therapy and patient conformance by targeting monitored release of phytoconstituents [22]. This chapter deals only with the related discussion of significant phytoconstitutional aspects due to lengthy and specialized conventional chemical drugs discussions.

Understanding and using herbal remedies came about when people could choose plants to feed and alleviate symptoms and diseases in different civilizations throughout human development. Conversely, traditional supplements were progressively replaced in the second half of the twentieth century by allopathic medicines, especially in the Western world. Therefore, allopathic therapies are presently more commonly utilized in industrialized nations than traditional remedies in particular. However, most underdeveloped nations are still using natural medicines, perhaps because synthetic medication is costly, and thus, 80% of developing countries rely on traditional medicine practices to satisfy their fundamental health needs or provide them with additional benefits, according to the WHO. Therefore, about 50% of the medicines authorized during 1981−2006 were directly or indirectly derived from natural sources [23]. WHO classifies traditional medicinal products as natural plant resources to preserve or disregard industrial processing in local or regional diseases. Drug medicines have been employed in developing and developed societies for centuries because they naturally occur and cause fewer side effects [24].

These bioactive components are almost named phytoconstituents or ethnopharmacology, protecting the plant against infections or pest infestations [25,26]. Without knowledge of plant cellular actions or chemical mechanisms, phytoconstituents have been utilized as drugs for the past centuries. The foundation of traditional medicine has become mainstream medicine worldwide; 80% of diverse ailments have been treated, independent of local or local applications and photo component techniques in this treatment. Bearberry and cranberries juice are used as a wide-spectrum antifreeze to treat urinary tract infections; lemon balm, garlic, and tea tree are simply a few examples of all sorts of human body use [27].

Due to the historical information of patients to now, maybe not always using the herbal medicine was excellent and beneficial for treatment because the herbal medicine: (1) taking too much time to act, possessing sometimes causes allergies, (2) not reliable to severe illnesses such heart attack and broken bones, (3) ineffective in sudden illnesses and accidents, (4) assisted with adverse side effects for certain disorders taking a long term to cure, (5) consisted of risky properties for their harvesting, and (6) failing the correct identification of the desired plants that can even direct to toxic effect.

Despite some of the above advantages of herbal/traditional medicine types, let us consider the following advantages as well:

1. The traditional formulas are more useful for long-standing health complaints, so they can be suitable for health with low side effects.
2. Due to minimal cost, some plants can even be planted in small houses.
3. Nowadays, obesity is a fundamental problem in various societies, and herbal medicine can be effective with the lowest risk.
4. Without a doubt, it is easy to find any desirable and necessary herb in any pharmacy or herbal store without a prescription to sell remedies for treating a coronary artery disease or even reduce cholesterol level in the bloodstream or heal a severe trauma.
5. Enhance therapeutic value, reduce the toxicity and side effects of medications and improve bioavailability are further benefits for plants rather than contemporary medicines.
6. It is taking a long time to cure diseases by plants. Anyway, be aware of buying fake herbal medicine, get advice, and consult experts and practitioners to ensure herbal medicines as alternative medicine are shiny aspects that must be considered for patient health [28,29].

3. Herbal medicine classifications

Herbal medicines (HMs) have been determined as constructions manufactured industrially and containing active components being net and naturally essential, not chemically modified plant materials, and are accountable for the product throughout treatment efficiency. Due to herbal production belief, the high cost and side effects of most modern medical treatment of different challenges worldwide lead to HMs being more assured and demanded than typical drugs. Therefore, consumers have turned back to herbal-acquired constructions. However, like typical drugs, HMs contain several chemical ingredients adequate to fabricate phytomedicine effects, creating mild and natural adverse reactions revolving from renal dysfunction, liver poison, high blood pressure, and even death. Health materials of HMs may also rise, while the production is tinctured with unicellular microbes, wort, or mold [28,30–32]. So the idea that herbal productions are safe and free from side harmful effects now is false.

In some countries, HMs' efficacy is more complex and challenging, and controlling the research protocols, standards, and methods is also needed.

Controlling the premarketing of drugs in drug regulatory authorities (DRAs) supports ensuring the safe use of whole drugs by fulfilling the excellent quality, safety, and compelling valuation former to their marketing. It means DRAs need manufacturing groups to witness good manufacturing practices (GMP), quality control, and poison tests to confirm the material's safety. However, an HM may be combined with mixed HMs with much toxicity. A state standardization, ethical and economic forces contain clinical efforts for HMs, restricting the capability to make firms perform the necessity of clinical action. The accident of high-profile health-related HMs, assisted with the obstacle to proving clinical action, ordered that DRAs regularly assess the situation to certify the health use and accesses of HMs in the marketplace. HMs are not considered drugs in various countries but as meals or dietary additions, requiring less precious regulatory evaluation than drugs. Here is distinguished a significant role of global regulations in determining and classifying HMs in small countries. To do so, the global registration of the imported product to define and classify a standardized approach is fulfilled using the recommendations presented in the global implementation leading to evaluate the quality, safety, and efficacy of DRA structure of imported HMs into the destination country, where HMs in the small public lacking the ability to produce their own HMs, are applied as foods or dietary supplements and less regulative evaluation than medicines.

Despite having similar plant products as HMs, under the pretext of seemingly healthy, superpower exporting countries such the United States, Britain, and Germany allow to evaluate the quality, improve obvious definition, classification, and policy strategies, stabilize and prepare recommendations for implementation of DRA structure of the same products, HMs, in the small countries, like Bahrain, the United Arab Emirates, and so on [33–36].

4. Herbal nano-drug delivery system

Individual compounds are never used since they are incompatible or have unfavorable characteristics with other formulations. Several nanotechnological techniques have been applied in this way, such as polymeric nanoparticles (NPs), solid lipid NPs (SLNs), liquid crystal systems, polymer-stabilized liquid crystals (PSLCs), liposomes, and microemulsions, which enable substances with various properties to be used in the same formula and can also alter the properties and actions of material in a natural setting. They have been attempting to break this barrier. The herb's pharmacological effects can be acquired only when condensate is confined within the treatment confine, while a little bit more or less than concentration is conducted to poison effects or no response. Therefore, it is clear that both the titration and definition of their dose are evitable. To overcome two

main problems of phytoconstituents (herbal-based drugs), including stability materials and low lipid solubility, the phytoconstituent DDSs are being created and expanded. The new DDs will boost the functional components' performance and reintroduce other scrapped components because they are not effective in their wording.

Scientists of herbal and nanomedicine have acquired NP therapy prepared as more impressive DDSs than traditional medical formations. Taratula's work [37] consists of advantages, limitations, phytochemical incorporation, and references to various nanotechnology delivery systems for selected phytochemicals such as NPs, solid lipid NPs (SLNPs), liposomes, carbon nanotubes, micelles, and dendrimers. Significant growth in their anticancer function resulting from nanotechnology advantages can be studied in Ref. [38]. Herbal medicinal products are supplied mostly orally due to easy administration and manufacturing convenience. Traditional herbal preparations can thus be classified as extracts, granules, pills, and capsules (Fig. 15.2 and Table 15.1). Oral absorption leads to many possibilities for delivering no toxic materials, and then there is specific attention to gain oral chemotherapy in oncology. Enhancement of CUR oral absorption using self-emulsifying (microsized scale) DDSs and increasing bioavailability of ubiquinone using self-emulsified (in nanosized scale) DDs [39,40] are examples for this purpose.

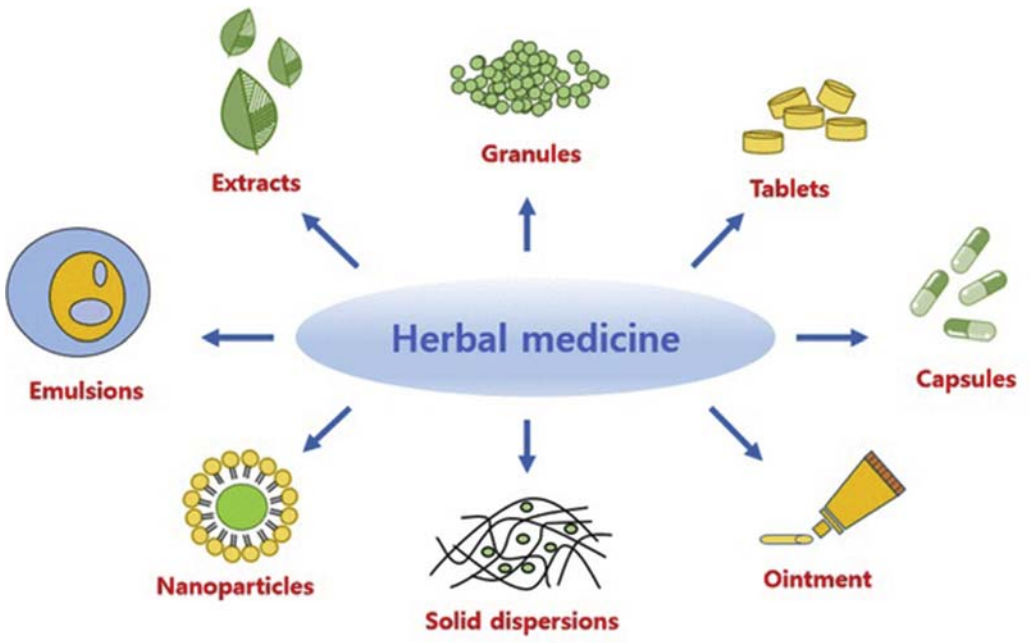

Figure 15.2
Schematic presentation of various herbal medicine formulations [41].

Table 15.1: Nano-herbal medicines with their formulation and uses.

Herbal	Carrier	Applications	References
CUR	Hydrogel NPs of hydroxyl propyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP)	Antimalarial	[42]
Leaf extract of *Mukia scabrella*	Biosynthesis of Ag NPs	Antimicrobial activity	[43]
A *Bauhinia tomentosa* Linn aqueous leaves extract	Biosynthesis of Au NPs	In vitro anticancer activity on decreasing the percentage (%) cell viability of laryngeal HEp-2 carcinoma cells	[44]
CUR and temozolomide implemented	Magnetic NP (MNP)-based drug-delivery approach for codelivering	Suppress tumor growth and prolonged long-term survival for glioma therapy	[45]
Syzygium cumini seed (ASc)	Polymeric NPs containing ASC (NPASc)	The anticancer characteristics not only triggered apoptosis and self-renovation capacity in colon cancer stem cells in early-stage HCT-116 but also induced HCT-116 (CSCs)	[46]
Medicinal herbs, sage, and savory extracts	Witepsol and carnauba solid lipid nanoparticles (WSLNPs and CSLNPs) phenolic compounds rich extracts	WSLNPs with a more acceptable herbal extract vehicle with high gastrointestinal consistency as well as a large phenol release proportion in the small bowel	[47]
(a) Persimmon leaf	(a) Stable self-nano-emulsifying DDS (SNEDDS)	(a) Substantial solubility, in vitro release, and bioavailability compared with NaoXinQing	[38]
(b) Optimized quercetin (QT)	(b) SNEDDS	(b) Superior liver injury protecting effect relative to QT against hepatotoxicity is caused by paracetamol.	[48]
(c) Seasol and linoleic acid	(c) Optimized SNEDDS	(c) There have been no toxic effects and protection against hepatotoxicity caused by paracetamol	[48]
(d) Zedoary turmeric oil (ZTO) extracted from the rhizome of *Curcuma zedoaria*	(d) ZTO-SNEDDS	(d) Lipid-phase with double advantages of increasing drug loading and minimizing the inert oils' requirement.	[49]

Continued

Table 15.1: Nano-herbal medicines with their formulation and uses.—cont'd

Herbal	Carrier	Applications	References
Chinese medicine Niuhuang Xingxiao Wan (NXW) with four units, as realgar, frankincense, and myrrh oil (FMO), musk, and bezoar	NXW multiunit drug-delivery system	Enhancement of bioavailability and efficacy. in vivo antitumor activity.	[50]
Four prenylated flavanones isolated from Eysenhardtia platycarpa leaves	Nanoemulsion and polylactic-co-glycolic acid (PLGA) NPs	Treatment of inflammatory disorders.	[51]
OA-loaded NPs	Poly(lactic acid) (mPEG-PLA), and mPEG-poly(lactic-co-glycolic acid), (PLGA), poly-encapsulated oleanolic acid (OA) (mPEG), as nanoformulation NP OA	Influence of cytotoxicity on cancer cell lines and cancer treatment due to apoptosis	[52]
The crude bark extract of *Tecomella undulata*	Extract loaded polycaprolactone (PCL)/ polyvinyl pyrrolidone (PVP) nanofiber mat	Wound healing or skin-bacterial infection treatment	[53]
Centella asiatica (CA)	CA (EGC) membranes	A potential material for wound dressings.	[54]

Moreover, by enhancing its selectiveness and power, preventing thermal or photodegradation, minimizing adverse effects, and regulating the release of active components, this procedure is much more desired till the therapeutic application is introduced or employed [55,56]. A novel DDS is intended to guide medicines, direct and retain the virginal medication, and favorably condense and enhance ill admittance. A new DDS is intended to guide medicinal products. Furthermore, different DDs are used in phytoformulation testing, such as liposomes, polymer NPs, microemulsions, spheres, and SLNs.

Composed lipophile is a chemical compound in a colloidal carrier form to dissolve in fats, oils, lipids, and nonpolar solvents used professionally to deliver the drug. These NPs are a solid lipid form at room and body temperatures with an average size from 50 to 1000 nm. As a result of the SLN, the carrier system reaches the specific site where the drug must be released [57].

Advantages of SLN herbal formulation

1. This formulation leads to release control and reaches the specific site where the drug must be released.
2. Both lipophilic and hydrophilic drugs loaded in this system can be produced on a large scale.

Today, smart universal purchasers would naturally prefer components in food, medicine, and beauty products as they have confidence in natural substances being assured and more practical, with common undesirable effects being known for ordinary people. Raising plant medicines' performance with better dosage formulations directs to the valuable plan of high technology and system known worldwide as DDSs for phytoconstituents [23].

A drug is a specific material fabricated from natural or chemical substances for diagnosis, treatment, or disease prevention. One of the sufficient subjects of the medical territories named drug therapy dramatically and mainly depends on efforts given knowledge in a pharmacological science while supporting the advancement in whole medical domains. They have played a significant role in increasing average life expectancy across the world. It has been continuously discussed from the point of view of therapeutics, economics, and production technique. Due to appropriate management, drug therapy also needs a pharmacy. Generally, medicine or a drug can be defined as a substance that contains essential natural sources from Plants, animals, microorganisms, or chemically synthesized, which has a physiological effect when ingested or otherwise introduced into the body [58]. That happens through inhalation, injection, smoking, consuming, absorption, or dissolving after using a drug, temporary physiological changes in the patient's body. Some can treat an illness by killing or halting the spread of invading germs, such as bacteria and viruses. Positive and negative effects can cause treatment or situate the body in dangerous/unfortunate effects. As a result, the right to know and deal with its effects is crucial—some drugs affect dividing or preventing multiplying abnormal cells, as in cancer treatment. Sometimes a part of the body cannot produce enough of a particular chemical. Therefore, some medicinal products replenish missing components or correct excessively low natural body chemicals, such as particular hormones or vitamins.

Drugs can be distributed in many ways, for example:

1. Fluids swallowed (i.e., cough syrup)
2. Ear and Eye drops
3. Skin rubbed with lotions, gels, or ointments
4. Nasal and asthma Inhalers
5. Transdermal patches
6. Tablets beneath the tongue (medication is absorbed into blood vessels and enters the bloodstream)
7. Injections or intravenous (inserted into a vein) medications

Due to less drug degradation, loss, and adverse effects, and improved drug bioactivity and the dense drug [59], there is an approach to deliver a drug with a significant effect and higher efficiency. Due to maximum benefit, some drugs with optimum concentration range must be delivered. Therefore, more or less, this concentration is always derived as toxic or with no therapeutic benefit whatsoever. Considering this new idea, a new discussion on

controlling the pharmacokinetics and dynamics, toxicity, immunogenicity, and optimum medicines' efficiency was created [60,61]. The most common methods of DDs provide various DD solutions, such as oral, parenteral and implant, pulmonary and nasal, transmucosal transdermal and topical DDs, delivery of proteins and peptides, DD pipelines, and DD deals.

A droplet under the tongue, sticker on the skin, and pump such as an insulin pump are only a few types of DDs. Some DDs are novel ways to DD addressing the limitations of the traditional DDSs. Considering date medicine and exactly treat important diseases using the targeting effect affecting the human body inside and delivering the medicine to the defective part. The required formulation, dose, mechanism, and effects, of medicines can be defined using pharmacokinetics, mechanism, and site of actions. These novel DDs can offer multiple DD ways such as Oral DDs, parenteral and implant DDs, pulmonary and nasal DD, transdermal and topical DD, for delivery of proteins and peptides, DD pipelines, and DD protocols [66].

This novel method DDS significantly delivers a drug with specific effects with maximum benefits for therapy without toxicity and harmful products. It is a novel idea that can control pharmacokinetics, pharmacodynamics, nonspecific toxicity, immunogenicity, biorecognition, and drug efficacy. The recent developments in DDs of herbals contain Phytosome, Liposome, NPs, Emulsions, Microsphere, Ethosome, SLN, Controlled DDS, other novel vesicular herbal formulations, Proprietary DDS of plant actives and extracts, Niosomes, Proniosomes, Transdermal DDS, Dendrimers, Liquid Crystals, and Hydrogels.

Recent patents on novel herbal formulation, including the novel system incorporated and active ingredients, and several US patents through some references are provided in Refs. [62–67]; various active ingredients and the incorporated novel system are briefly introduced in Table 15.2.

Table 15.2: Brief introduction of US novel plant patents.

US patent no.	Active ingredient	Novel system incorporates
US 6340478 B1	Ginsenosides	Release formulation microencapsulated and controlled
US 5948414	Opioid analgesic and aloe	Olfactory spray
US 6896898 B1	Alkaloids of *Aconitum* Sp.	Transdermal system of delivery
US 6890561 B1	Isoflavones	Formulation of microcapsules
US patent 2007/0042062 A1	Glycine max containing 7s globulin protein extract, CUR, *Ginger officinalis*	Herbal tablet dosage form

Curing different diseases with fewer side effects (e.g., toxicity) and better therapy are caused that phytoconstituent DDs are considered much more attractive and trustable in the brand-new world.

These herbal remedies contain hundreds of phytoconstituents present novel materials against the diseases. Thus, the development of herbal drugs due to people's increased interest in phytopharmaceuticals because of the global market, cost, long term use, natural/eco-friendly, no adverse drug effects in general, readily available is needed [68–70]. Herbal drugs and their derived constituents on the global market are included Lovastatin (anticholesterolemic) [71], paclitaxel, doxorubicin (both anticancer drugs), cyclosporine-A and tacrolimus (both immunosuppressive) [72], erythromycin, streptomycin, rapamycin (all antibiotics), and amphotericin-B (fungicidal). Actually, concerning conventional phytopharmaceuticals, plant types of drugs are naturally derived from plants and remedies. Additionally, numerous drugs, such as digoxin, quinine, morphine, atropine, aspirin, bromelain, salbutamol, and colchicine, have been extracted from the plants with their active molecule healing various diseases [17,73].

For instance, the turner was extracted from morphine (from the ancient Greek of Morpheus, meaning god of the dreams) from the opium poppy (*Papaver somniferum*) in the 18 century. Practical medicine is an example of these drugs that can play an influential role in beings' lives, introduced "Morphine." Morphine in pharmacology is administered intravenously, rectally, subcutaneously through spinal injection and inhalation. This substance's main remedial activity reduces pain, while it can relieve acute and complicated chronic aches. Anxiolysis, euphoria, and making sense to relax are also other morphine effects. Morphine has remained the unique solution to choose acute myocardial infarction as it severely rescues patients from pain and eventuates in remarkable peripheral vasodilatation and decreases in bodily vascular insistence. This drug is extremely impressive in cardiogenic pulmonary swelling as it pauses the sick and deduces dyspnea and heart muscular oxygen request [74].

5. Roles of nanotechnology in herbal medicines

Recently, the significance of NT has surprisingly varied its results for biomedical uses, whereas NT has reconstructed many scopes with its appreciable capacities and ground-breaking novation. Nano technical substrates have presented considerable inflection confinement by refashioning conventional experiences and discovering novel effective medicine methods.

For example, considering applying *Aloe vera* (AV) in the formation of hydrogels, NPs, nanocomposites, and nanofibers, and bioinspired sponges have developed their right-appointed use perspective within the scopes of wound treatment, tissue engineering, and

DD. The maturing benefit in purchaser and producing materials based on green or eco-friendly approaches also extremely persuades the applying of numerous plant-based natural materials involved AV. From the past until now, AV's abilities as a promising remedy are used for several ailments not only for scientists' investigations of its unplumbed abilities and meritable medicinal but also commercial use helping significant industry roles potential in the market. Today, scientists apply this natural benefit source in nanoengineering that has revived novel composites and biological features while influencing biomaterials' macromolecular features. Consequently, AV has produced a potent correlation compared with the traditional material chemistry peers and now plays a significant role in the product's accuracy in both characterization and treatment fields [60,75]. New-day Aloe vera demands generating soft and hard tissues (such blood vessels, skin, and bones) based on biological matters are growing, whereas AV is more biocompatible, nonpoisonous, eco-cost and generates essential nutrients for locular skin and scaffolds rebirth [76].

The medicine plans are affected (Fig. 15.3) by metabolites or organic compounds produced using herbs and plants through metabolic pathways, while there are considerably enzyme-mediated chemical reactions. These plant metabolites consist of initial and secondary metabolites, whereas the herbal compounds possess essential and particular functions. In this way, phenomena such as growth and development included initial metabolites are mentioned in initial functions, and pollinator tension or defense versus herbivores in particular functions included secondary metabolites.

Depending on the plant's community, the patient can get rid of pain or illness such as fever, asthma, constipation, esophageal cancer, and hypertension, helping traditional medicinal plants [77]. These drugs are available, while an appropriate form with specific safety, efficacy, and acceptance is considered. For example, the dose or DDs is usually defined as well as the formulation of other factors.

6. Nanocarriers for herbal medicines

Unique physical and chemical features of NPs offered extensive development for applications to treat diseases with their sufficient effects in the DDs [79,80]. The safety and long-term effects of nanostructural materials not overlooked have been supernaturally producing many advances, especially in medical and pharmaceutical applications. Therefore, advent promotions in particular recent years led to a significant reengineering innovation improved pioneer affect factors controlling more efficiency. Proponents of this versatility technology fabricated by the human-made demonstrate a novel revolution of machines and medicines as commercial products. Richard P. Feynman's concept often describes the primary NT.

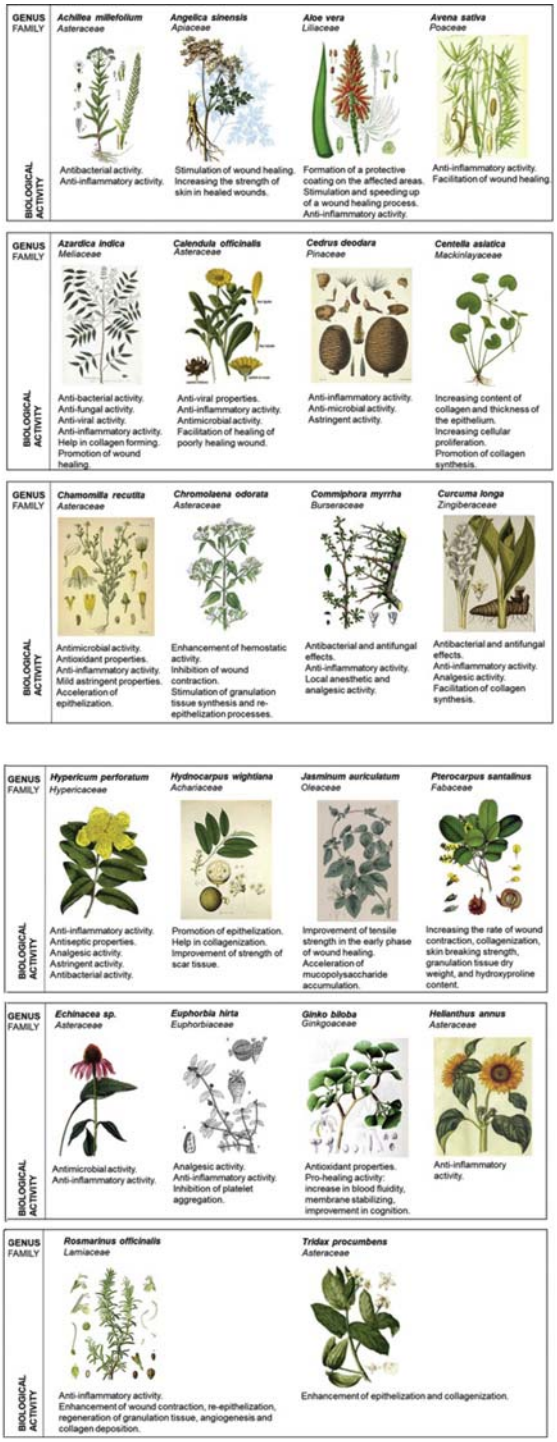

Figure 15.3

Major genus families and biological activities of plants applied in drug medicine, with the potential applications explored in this chapter [78].

According to A. K. Sachan's forecast, nanopharmaceuticals were accumulated from active phytoconstituents/extracts, permitting the nanomedicine market world to be estimated at $130.9 billion in 2016. AS a result of this report, they have active bases of sea worth, cassia twig, and licorice root cause to be more effective in treating pulmonary, liver, bone, and skin cancer and Kaposi sarcoma. Nanomaterials can also predict and diagnose some diseases for beginnings starts and very early stages, such as colonies breast, lung, colon, prostate, and ovarian cancer [81].

DD improvisations. The majority of existing NT chemotherapy systems included repackaging conventional anticancer drugs to various kinds of nanometers. NT has developed new concepts and suppliers that traditional technologies cannot deliver. The study explores how nanotechnology applies to the formulating of DD mechanisms for such herbal anticancer agents [vincristine (VCR), etoposide (ETP), paclitaxel (PTX), resveratrol, CUR, CPT, quercetin, genistein, and capsaicin (CAP)] leading to a more robust anticancer profile [37].

The structures of nanodrug carriers would state that the hepatic may be metabolized, and therefore, blood cannot enter the blood by not carrying the ideal quantity of herbal drugs in the high acid pH of the stomach and other constituents. Therefore, therapeutic effects will not be met by reducing the dose (to levels below on optimum amount) to the infected region. Nanosized carriers offer a way to cross biological barriers such as acidic pH of stomach and liver metabolism and increase the drug's prolonged circulation into the blood due to their surface area to volume ratio [1,82]. This system attempts to decrease systemic toxicity and pharmacokinetics and biodistribution and provide controlled release kinetics to the target site.

This novel system demonstrates the growth of stability, maintained release of formulation, preservation of toxicity, and much higher treatment efficacy. This progressing alternative's final purpose, meaning DDS is to enhance efficiency, provide a nondestructive process, and provide more patient relief. The present study will highlight brief information about the significant role of nanosized particle formulations on phytoconstituent NDDSs and the impact on treating patients' diseases.

It is possible to describe most advantages of plant NPDS can be summarized in the following:

1. The plant formulation is directly delivered to the site by NPs,
2. Efficacy and therapeutic effect are enhanced,
3. Stability is enhanced through encapsulation,
4. The pharmacokinetic effect is improved,
5. Various sizes, compound surface properties can be produced.

Disadvantages of plant NPDS can be included in the following:

1. NP tends to be wrapped in reticuloendothelial system cells and delayed release by phagocytes when endocytosis, fusion, surface adsorption, or lipid exchange stabilizes the liposomes.
2. There is difficulty stabilizing the formulated liposomes that many studies now view as following appropriate approaches to solving this problem.

Numerous developments in recent years, nanosized carrier systems made from biodegradable and nonbiodegradable polymers, like liposomes, SLNs, polymeric aggregated molecules in a colloid, and so on, have been studied for their ability to transport anticancer medicines. Some advantages of nanosized materials create more stability, long-term lasting, more solubility of components, improved absorption for drug composition, and less dosage. NPs at nanoscale/subnanoscale are structures combined with polymers [61]. The colloidal systems in nanosized scales are less than 1000 nm. A useful site is built using the encapsulated effective system. Moreover, the protection of drugs/foods is accrued effectively through microencapsulation of plant extract in NP. Microencapsulation of plant extract in NPs is employed to protect drug or food ingredients against deterioration, losses, or raw interaction with other materials [83].

A key role is the nanotechnological approach employed in herbal medicine, and more significantly, in DDS adjusted to fast spread. Compared with conventional therapies, NDDS with nano-herbal formulations can be considered more precious. An example is the ability of nano-herbal DDSs to enhance activity and overcome the problems associated with medicinal plants. Therefore, these herbal carriers with nanoscale sizes can help recover dangerous diseases like cancer, diabetes, etc. [84] Considering the lack of scientific explanations and processing problems for herbal drugs, there was no growth of formulations for the long term. However, new phytopharmaceutical research could find prepared answers for the scientific requirements (like pharmacokinetics defined, mechanism and site of actions, dose amount required, etc.) of DDSs involved NPs, matrix systems solid dispersions, liposomes.

Among the extensive types of vascular deliveries formulated, such as liposomes, phytosomes, ethosomes, and so on, the synthesis of particles nanosized has additional features, including safety and long-term effects in the case of phytoconstituent DDSs. With the sufficient growth of NT in recent decades, appropriate delivery approaches for nanoscience have been provided. NPs in a tissue organ or special cells are significantly offered as potential candidates to carry the therapeutic agents safely into a crucial target area (chamber) for drug acting. This innovation may solve the challenges between two current and future DDSs. In other words, the NPs are changed into drug tablets on a nanoscale while they can be loaded with a gene or drug agent and can considerably treat some diseases—for instance, cancers.

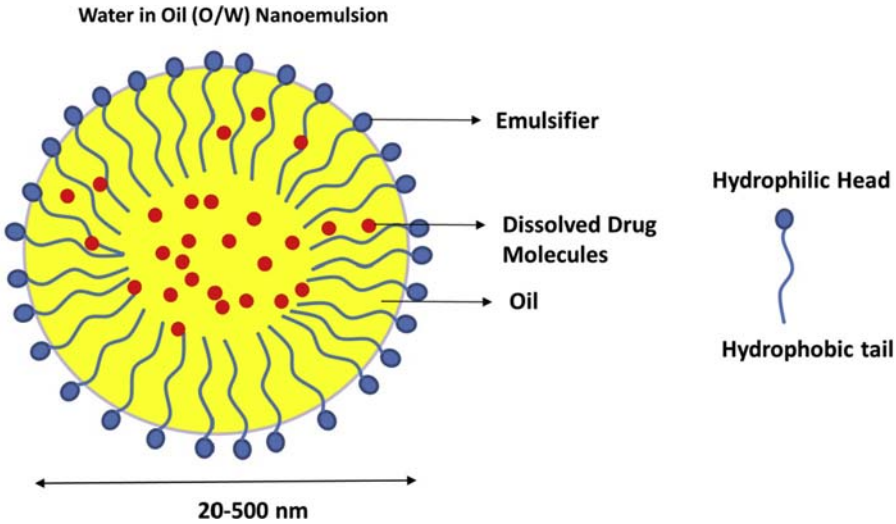

Figure 15.4
Schematic illustration of nanoemulsion, highlighting the phospholipids' basic assembled unit with the packaged drug molecules within the oil layer [85].

Oral chemotherapy in oncology has been recently developed due to the nanosized carrier's sufficient potential such as nano polymers, SLN, polymeric micelles, nanoemulsions (Fig. 15.4), etc., cytotoxic agents of the drug can be delivered for curing cancer.

Plant drugs and phytoconstituents have been combined into emulsions for various targets, changed from nano to micrometers using homogenization and fluidization in high pressure. An adequate system of NPs as fast and easy the encapsulated in colloidal systems in nanoscale to subnanoscale sizes (10−1000 nm) of a synthetic/semisynthetic polymer can also be reached the practical site. The encapsulated herbal extract in a microsized structure is now known as a trustable and sufficient way to protect food/drug against loss, degeneration, or other biodiversities [61,83]. Two-phase liquids such as water and oil droplets are frequently dispersed from 0.1 to 100 μm and are named microemulsions/nanoemulsions, being stable and isotropic, helping a surfactant thermodynamically [86]. The advantages of this process can be summered as fellow: (1) Due to a tight formation, nano/microemulsion can be released and direct contact with body tissues for a long time without any side effects; (2) Oil-water-oil emulsion makes lipophilic drugs, and this concentration increases in organs such as the kidney, spleen, and kidney; (3) Comparative illustrations of the nanoemulsions preparation process were presented by Ranjit [87], in a detailed overview of Fig. 15.5.

NE as an approach used for transdermal DD, this schematic shows how NEs effectively deliver both lipophilic and hydrophilic medicines via skin layers to attain the bloodstream, using the favorable therapeutic effect (Fig. 15.6).

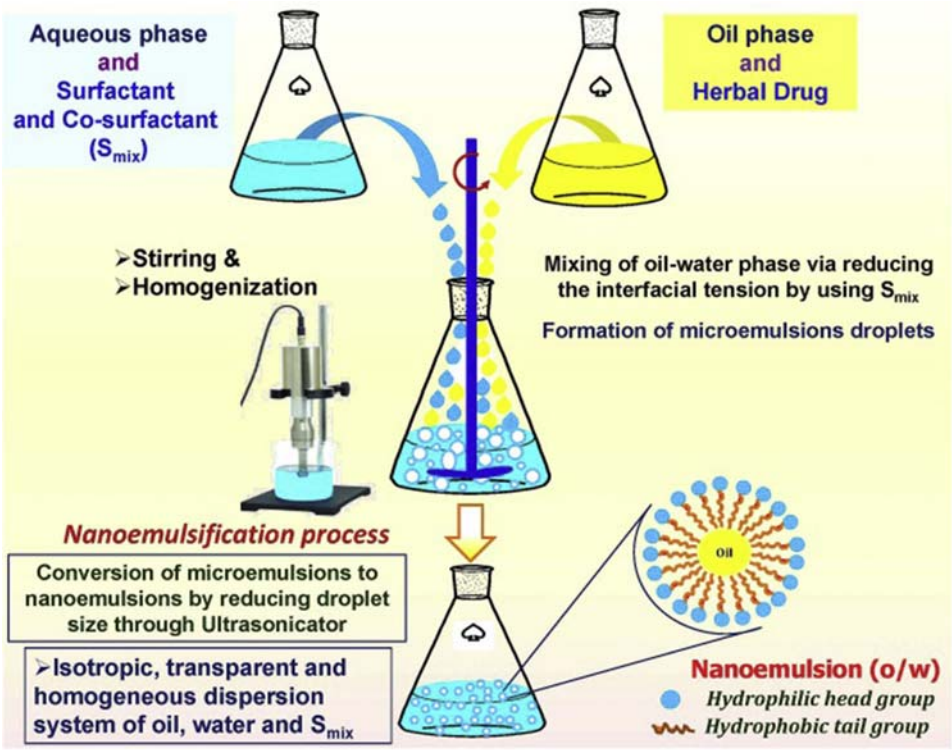

Figure 15.5
Comparative illustrations of the nanoemulsion (NE) preparation process [87].

Some plant drugs and phytoconstituents have been combined into microemulsions and nanoemulsions for various DDS applications shown in Table 15.3. Compared with traditional emulsion, the oral absorption of curcumin (CUR) and the solubility (bioavailability) of the ubiquinone have been increased using self-microemulsified and self-nanoemulsified DDSs, respectively. In addition, (see Table 15.3), using a self-nanoemulsifying DDS, the precipitation of plant drugs in the vehicle decreased. Some literature involving herbal micro/NE is in Refs. [11,39,40,49].

Improvement in nanotechnology CUR bioavailability, enhancement of nanocapsule zedoary turmeric oil, and decreased toxic effects from NP paclitaxel have been reported by Refs. [95–97], respectively. Table 15.4 dedicates some NP herbals controlling released and target medicines from DDSs for different tissues/organs. Recently, various Paclitaxel-loaded Polymeric NPs to reduce the side effects of DDSs against cancers are also listed in vivo and in vitro considered in Ping Ma, 2013 [98]. Regarding the revolution in all the different domains of science and technology, dose forms have enhanced from simple pills to novel DDSs demonstrated as an ultra-high sophisticated technology, the system

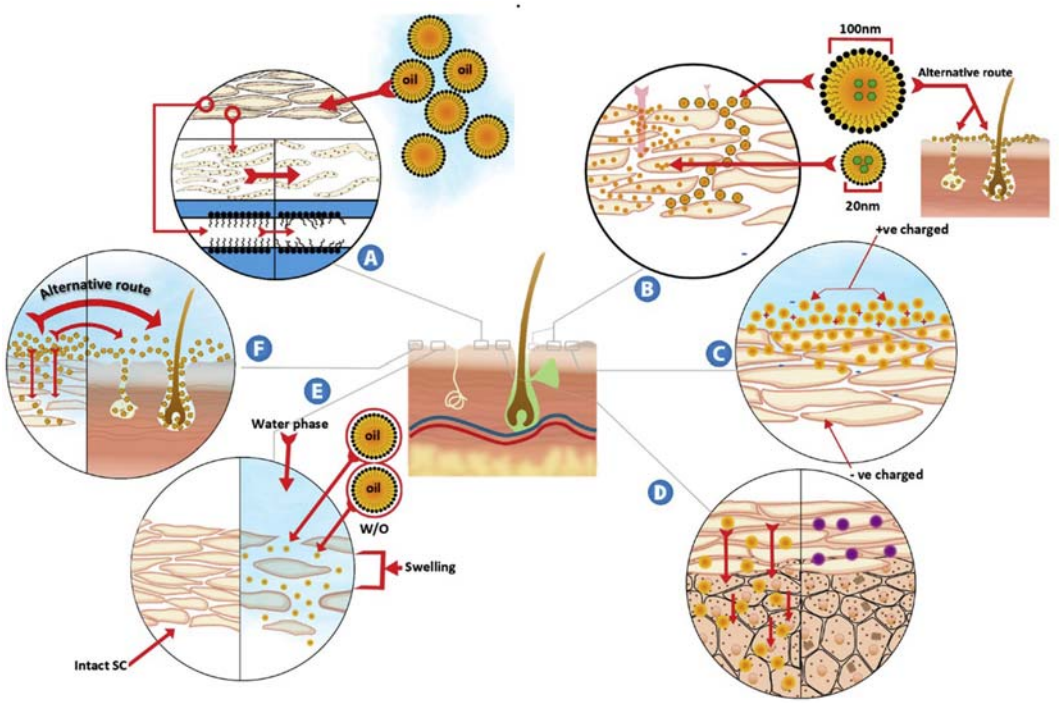

Figure 15.6

Hydrophilic nanoemulsion (NE) transdermal improvement: (A) Improved thermodynamically active drug operation. (B) Improvement in the electric surface load of ionic medicines. (C) NE components to promote the delivery of sebum solubilization. (D) the direction of the big molecules, which are water-soluble, filled in w/o NE. (E) Bring in o/w NE for follicular distribution of small water-soluble molecules [88].

Table 15.3: Herbal microemulsion/nanoemulsion.

Herbal drug	Purpose
Curcumin (CUR)	Oral bioavailability enhancement
Self-nanoemulsified drug delivery system of ubiquinone	Improved solubility, bioavailability, and precipitate precipitation in the vehicle
Zedoary turmeric oil (ZTO)	Aqueous dispersibility improvement, stability, and oral dispersibility
Submicron docetaxel emulsion (SDE)	Improved residence time for improved action against cancer
Berberine nanoemulsion (BBRN)	Improved period for residence, absorption, and improved action of cancer
Quercetin microemulsion (QM)	Increase in the corneal and epidermal stratum; better action of antioxidants

Table 15.4: Some nanoparticle herbal drug-delivery systems to control release and targeting of drugs to organ tissues.

Herbal drug	Medicinal uses	References
AV, CU, and neem (*Azadirachta indica*)	Cell lines of copulatory cancer of the human breast (MCF7) and lung cancer (A459).	[89]
Biosynthesized 5-fluorouracil (FU) nanoparticles (NPs) using AV extract NPs	Against human adenocarcinoma colorectal cell lines (HT-29 and Caco-2)	[90]
Triblock polyethylene glycol (PEG)-polybutylene adipate (PBA) nanocapsule loaded with AV extract	Cosmetic and ulcers or cancer treatments	[91]
NP curcumin (CUR)	Effective against malignant brain tumors.	[92]
NP CUR	Effective against cancer	[48,93]
NP CUR	Five times more activity against breast cancer cells than CUR in inducing apoptosis.	[94]
CUR and temozolomide loaded magnetic NPs	Anticancer and antitumor activity	[45]
Zedoary turmeric oil	Increased drug loading decreases the inert oil requirement anticancer, hepato-protective.	[49]
Flavonoids (quercetin and kaempferol)	Improvement in bioavailability, antioxidant and anticancer.	[38]
Quercetin	Protective effect against paracetamol-induced hepatotoxicity.	[48]

minimizing drug degradation and loss, protecting unwanted and adverse effects and growing drug bioavailability and the drug accumulation controlled in the recent decades, all over the world [59].

Hence, the use of this plant in the formulation of hydrogels, NPs, nanocomposites, and nanofibers, and bioinfused sponges has prolonged its acceptable appointed use spectrum in the scopes of wound curing, tissue engineering, and DD. Particularly in the formation of biomaterial-based structures in nanosize and these dramatic features of AV relief the industrial players to identify its massive potential and afford many Aloe products to the Bazar. These are the rising interest in expanding and fabricating AV materials based on green or eco-friendly manners [60].

Oral doses and uncontrolled doses can be useless and even toxic. Because in typical doses, these factors often disappear during intestinal transplantation or inadequate absorption. It means that it is ineffective. In addition, uncontrolled levels of these factors can lead to aging accumulation that affects the body. However, these small therapeutic agents' connections to NPs may solve many of the challenges of delivering and producing pills. Delivery systems for NPs, due to their small size, can penetrate the width of the barrier, through small capillaries, into individual cells for sufficient drug accumulation in

target locations within the body. Unezaki et al. believed that this would substantially reduce the agent's drug toxicity and increase the efficacy of the treatment by reducing the side effects of the medicine [99].

Nanocarriers suggest beneficial delivery ways for mixed anticancer treatment needed using a particular parameter for the microsized tumoral environment called the development of multidrug resistance (MDR) cancers. The nanocarriers consist of some possibilities such as response to being tailored to acquire multiple matters using a single set, amend the treatment index of medicines, and confidently modify their pharmacokinetics profile. They confidently gather in the tumoral microenvironment through the mechanism of the enhanced permeability and retention (EPR) effect, their ability to be intermixed to targeting half parts, and confused medicine flow by preferably local factors in the cellular perinuclear zone, out of layer local flowing pumps. Obstacles limit these types of medicine's efficiency and render it the motive power to plan novel delivery systems to decrease the ADRs and amend the clinical effect of existing drugs. It has also stimulated completed research activity to expand new analogs of present nature-derived drugs, amplify search for new combinations from natural sources, and apply nanotechnology manners to reclaim the security and influence profiles of these kinds of medicines [100].

Due to enhancing the EPR in the nanostructural targeting systems, the carriers loaded in the nanoscale region with their poisonous agents were added to the tumoral environment. Thus, improved medicines and DDSs are continuously growing in cancer therapy with beneficent consequences using nanostructure approaches to significantly diagnose and treat numerous cancers [101,102].

The definitions of nanomaterials, but it should be noted that there are two reasons professional researchers and scientists cannot comprehensively understand the toxicological evaluation for NMs decrease in the size distribution of materials with along shifting phenomena in the physical or chemical properties, having little data on the safety and toxicity of NMs.

This present chapter will treat numerous illnesses and cancers using DDSs by NPs, and some challenges will be reported only among developed experiences. A specific drug contains the primary purpose to miniaturize a target for the fast culture of nanoscaled biotechnology in very small DDSs. There is a novel therapeutic way when nanomaterial products with therapeutic agents by conventional DDSs (e.g., oral and injectable methods) can treat the patients.

Among different references studied, the following Tables 15.5 and 15.6 separately review the proper approaches to producing the NDDSs.

Table 15.5: Polymeric nanoparticle-based herbal medicine.

Herbal	Nanopolymer	Uses	References
Paclitaxel (PTX), and etoposide (ETP)	MG63 and Saos-2 osteosarcoma cell lines	To prolong the blood circulation time against osteosarcoma cancer cells	[103]
CUR	Cross-linked and random copolymers of N-isopropyl acrylamide (NIPAAM)	Free curcumin against human pancreas cancer in vitro therapeutic efficacy lines of the cell	[95]
Luteolin	PLA-PEG	Higher antiproliferative activity against H292 cells of lung cancer cells with lower IC50-values than free luteolin	[104]
Resveratrol (RSV)	Consisting of a poly (PCL) and poly(C, L-lactic-co-glycolic acid) (ethylene glycol) conjugate biocompatible mixture poly(EPGA) (PLGA-PEGCOOH)	Improvement of cytotoxicity compared with free RSV on DU-145 cell line on LNCaP cell line, and on the PC-3 cell line in prostate cancer	[105]

Table 15.6: Solid lipid nanoparticle-based herbal medicine.

Herbal	Lipid type	Uses	References
Paclitaxel (PTX) (from taxane tree)	1, 2—Solid lipid nanoparticles	1—Deliver cytotoxic drugs such as doxorubicin, idarubicin, PTX, camptothecin, 7-ethyl-10-hydroxy-20(S)-CPT, ETP, fluorodeoxyuridine, and retinoic acid, and cholesteryl butyrate	1. [106]
		2—Act as free drug formulation using murine breast cancer mice model with significantly smaller tumor size and lower Percent inhibition	2. [107]
	3—Star-shaped cholic acid-core PLA-TPGS copolymer	3—Both in vitro and in vivo, effective strategy for breast cancer Treatment	3. [108]
Luteolin	Monomethoxy poly(ethylene glycol)-poly(3 caprolactone)	To enhance the bioavailability and cytotoxicity	[109]

For example, according to magnetic NP-based herbal medicine, the quercetin (QUR) herb within the nanopolymers of MNPs with PLGA has been applied for optimized nanoplatform technology drug-loaded nanoparticle delivery in lung cancer using an aerosol formulation [110] (Table 15.7).

Table 15.7: Micelle-based herbal medicine.

Herbal	Micelle type	Uses	References
Luteolin	MPEG-PCL	Enhance the bioavailability and cytotoxicity	[109]
Lapachone	PEG-PLGA	Prolonged blood circulation and a higher concentration of b-lapachone and DNA damage and PARP-1 hyperactivation	[111]
CUR	Methoxy-poly(ethylene glycol)-poly (D/L-lactide) (mPEG-PLA)	Efficient nanocarrier for human brest	[112]
Honokiol	Poly(MPEG) and poly(3-caprolactone) 1 Monomethoxy poly(ethylene glycol) (MPEG); (PCL) (PCL) 2 poly(3-caprolactone)-poly(ethylene glycol)-poly-copolymer(3-caprolactone) (PCEC)	1 To enhanced dose related cytotoxicity on the CT26 colon carcinoma cells 2 To treat lung cancer	1 [113] 2 [114]

Due to physical and biological features, NPs have the novel capability to target tumors and dominate MDR using addressing of P-gp on anticancer effect ideas. This is done while coencapsulated cytotoxic agents with P-gp inhibitors together into NPs to stop the P-gp flow using the enrichment of antitumor medicines in tumors. Additionally, there are problems in some clinical uses of P-gp inhibitors, including verapamil, quinidine, cyclosporine-A, PSC833, VX-710, and limitations such as their unacceptable toxicity, variable pharmaco-kinetic interactions with the anticancer medicines, and interactions with other transport proteins. P-gp is expanding distributed in the intestine, lung, kidney, liver, adrenal gland, blood–brain barrier, and placenta, and has an abiotic role of the regular biosystems. It can result that the development of a modern DDS without P-gp inhibitors looks better, but it is necessary to have an antitumor effect similar to the coencapsulated DDS. As a clinical point of order, except P-gp, there are other reasons, such as cellular interaction, drug dissolution, cellular adhesion corroborating in close relationship with MDR. There, it seems there is no way to decide the MDR problem. It is recognized that human bodies and bacteria. Most organisms (including humans and bacteria) assign a set of MDR mechanisms similar to the tumor. This self-defensive system (SDS) assists whole existences to maintain when met with toxic agents after numerous years.

Nevertheless, the MDR cells will be destroyed in the microenvironment of the medicine while whole the MDR mechanism will not task more. Conjugated liposomal DDS can solve the obstacles mentioned above by increasing the medicine concentration in targeted zones, inducing SDS collapse, while the MDR will be killed [115]. Some cited papers are listed in Table 15.8.

Table 15.8: Liposome-based herbal medicine.

Herbal	Liposome type	Uses	References
Vincristine (VCR)	1 PEGylated folic acid	1 Significantly strengthened the antitumor efficacy	1 [115]
	2 DSPC/cholesterol	2 Enhance VCR toxicity and improve drug accumulation at tumor sites	2 [116]
Ursolic acid	pH-sensitive liposomes	To improve better anticancer activity of the nanoliposomes	[117]
	Thymoquinone	Proliferation of MCF-7 cancer cells and exerted very low toxicity on normal periodontal ligament fibroblasts	[118]
Lipid compositions	Berberine	Enhanced cytotoxicity compared with free berberine	[119–121]

A property of this polymer is that its structure and hydrophilicity can be precisely and easily controlled, while their forms obtain higher solubility, permeability, biocompatibility, biodistribution, clearance, and accordingly decreasing side effects. Nevertheless, dendrimers have lately been worked as carriers as they can be advanced in different forms, sizes, and surfaces, to achieve functionalized nanoscale formations (Table 15.9). Therefore, the dendrimer can suggest targeting ligands to improve particular binding to cellular receptors. In addition, the small dendrimer size allows it to be immediately cleared from the body through the renal and run away from the reticuloendothelial system. In addition, dendrimers' vast inner hollow let them mix hydrophobic medicines either by covalent or noncovalent conjunction. It seems that whole generations' dendrimers positively affect solubility increase and in vitro quercetin dual releasing pattern of a primary quicker release than sustained release. Further, the efficiency of this dendrimer on a carrageenan-decrease foot edema pattern to measure the sharp act of this nanocarrier in response to inflammation was also measured [127,128].

Table 15.9: Dendrimer-based herbal medicine.

Herbal	Liposome type	Uses	References
CAP	Dendrosome	In vitro anticancer activity with significant antitoxicity	[122]
Gallic acid with	Polyamidoamine (PAMAM)	To enhance cytotoxicity on breast cancer cells	[123]

7. Application of herbal nanomedicines

7.1 Anticancer

The long-term use of traditional DDSs for cancer chemotherapy drives the mortal destruction of normal proliferating cells. This is exclusively applied to manage solid tumors, where most tumor cells are not forayed rapidly. A targeted DDS is a system releasing the medicine at a preselected site in a defined method. Nanotechnology-based DDSs manufacture a remarkable afford cancer therapy, and the herbals play a vital role in expanding NP carriers to treat cancer. Some significant technological expansions of nanotherapeutic NDDS contain protracted half-life, reclaimed biodistribution, enhanced circulation time of the medicine, controlled and sustained release of the medicine, compatibility of track of administration, enhanced intercellular concentration of medicine, and many more (Fig. 15.7 and Table 15.10).

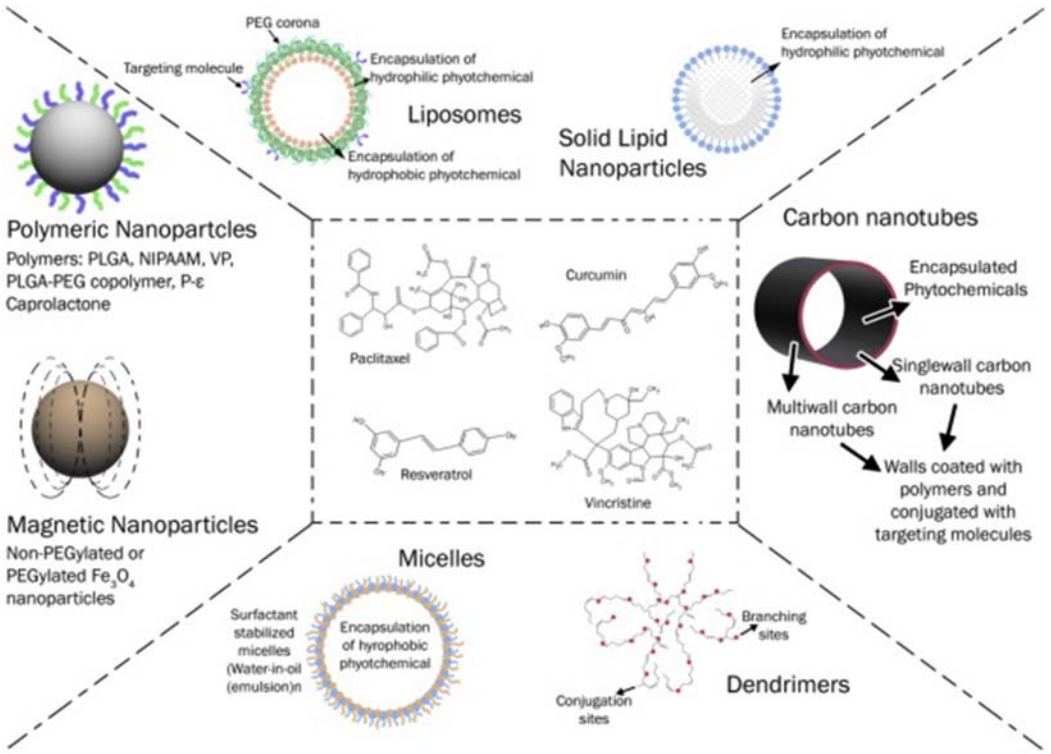

Figure 15.7
Schematic illustration of versatile drug-delivery systems for anticancer phytochemicals [124].

Table 15.10: Herbal nanomedicine applications in anticancer drug delivery.

Herbal	Nanomaterials	Uses	References
VCR	VRP poly(lactic-co-glycolic acid) (PLGA)	To reduce toxicity and enhance antitumor activity in multidrug-resistant breast tumor	[125]
Apigenin	PLGA	Better potential for use in the therapeutic management of skin cancer	[126]
Paclitaxel (PTX)	ETP coloaded polymer	Synergistic activity against osteosarcoma cancer cells	[103]
PEG	PLA NPs of epigallocatechin-3-gallate (EGCG)	Phases of cell cycle arrest with cyclins D1 and D3 regulation of the EGCG NP expression	[127]
PLGA	ETP	Increasing antitumor performance of ETP significantly and having a viable parenteral ETP, the formula avoided the drawbacks	[128]
PTX	PLGA	Significant cytotoxic effect relative to PTX alone	[129]
CUR	Micellar aggregates of cross-linked and random copolymers of N-isopropyl acrylamide (NIPAAM)	To enhance the solubility profile of CUR in therapeutic efficacy against human pancreatic cancer	[95]
Human serum albumin (HSA)	Noscapine	To reduce the cell viability of breast cancer cells	[130]
PTX	Star-shaped cholic acid-core PLA-TPGS copolymer	A potentially promising and effective strategy for breast cancer treatment	[108]
Luteolin	Polymeric NPs comprising PLA-PEG	A higher antiproliferative activity against lung cancer cells	[104]
RSV	1—Nanosystems, composed of a biocompatible blend of poly(epsilon-caprolactone) (PCL) and poly(D,L-lactic-co-glycolic acid) poly(ethylene glycol) conjugate (PLGA-PEGCOOH)	1—Significantly improved the cytotoxicity in prostate cancer cells	1—[105]
	2—Cationic chitosan (CS)-and anionic sodium alginate (Alg)-coated PLGA	2—Higher cytotoxicity against malignant glioma cells in prevention of (1) skin cancer (2) skin cancer and prostate	2—[105,131]

Continued

Table 15.10: Herbal nanomedicine applications in anticancer drug delivery.—cont'd

Herbal	Nanomaterials	Uses	References
Ferulic acid	PLGA	The increased anticancer effect in cell lung carcinoma	[132]
CUR	Chitosan	A higher cellular uptake and enhanced reduction in the cell in breast cancer	[133]

7.2 Wound healing

The wound healing (WH) process is a complicated track of well-orchestrated biochemical and cellular phenomena to reform the accuracy of the skin and hypodermic textile. Numerous plant extracts and their phytoconstituents are recognized as alternatives to wound healing agents for their multiple active ingredients, simple disposal, and limited ADR. The expansion of nanotechnological approaches can assist in promoting the effect of various therapeutics and herbal-based products. Various pharmacological aims are implicated by the WH effects of herbal-based nanoformulations, containing repressing the manufacture of inflammatory cytokines and inflammatory conduction waterfalls, decreasing oxidative parameters and increasing antioxidative enzymes, and improving neovascularization and antigenic routes across enhancing the presentation of vascular endothelial development parameter, fibroblast development parameter, and platelet-derived development parameter (Table 15.11). Further, nanoformulation of herbal extracts and their phytochemicals can increase their bioquality, control their release in the structure and shape of maintained DDs to the wound site and increase the penetrance of these treatments

Table 15.11: Herbal nanomedicine applications in wound healing.

Herbal	Nanomaterials	Uses	References
AV	Hydrogel made of poly (vinyl alcohol) (PVA), and poly(N-vinylpyrrolidone) (PVP) mixture	Completely cure rats within 15 days even without predressing	[134]
AV	Electrospun polycaprolactone (PCL)-AV nanofibers	In vitro, AV with along NFs with higher cell affinity, adhesion, and proliferation of human dermal fibroblasts (HDFs), and MTS demonstrated adhesion and proliferation rate compared with levels of AV	[135]
AV	Ag NPS using AV extract	Against *E. coli* and *Bacillus* Species	[136]
AV	In_2O_3—ZnO-AV nanocomposite	Activity against a series of bacterial and fungi stains	[137]

to the layers of the underlying skin, being all essential to treat. Different herbs extracts and their inherent compositions, applied in nanoformulations, have high activity in managing wounds and can be much more applied as future pharmaceutical medicines.

7.3 Tissue engineering

Nanostructures and nanophases at numerous categories of nanotechnology science play a significant role as a bridge of biology, physics, chemistry, materials sciences, and primarily nanomedicine-based DDSs. These materials can be characterized and recognized even with their sizes and shapes influencing the borders of nanomedicine, starting from biosensors, microfluidics, DD, and microarray tests to tissue engineering. The protein-based NPs are chemically changed due to the composition of the targeting ligands identifying precise cells and tissues to advance and enhance their targeting mechanism. One of the main disadvantages of using polysaccharides in the nanomedicine category is their oxidation specifications above the melting point, which is mainly needed in industrial processes. Moreover, most polysaccharides are dissolved in water, limiting the application in some categories of nanomedicine like tissue engineering. However, cross-linking techniques related to the polymer chains have been applied to guarantee the stability of these chains that assure them stability in liquid surroundings [12]. Table 15.12 shows some herbal nanomedicines used in tissue-engineering applications.

7.4 Antioxidants

Using herbal medicines in the nanocarriers will grow its potential for curing different severe illnesses and health affairs. It is organized that numerous prosperous examples with practiced traces are provided among us in the directions of nano studies. Herbal medicines are also favored resources of beneficial compounds maintaining antioxidants and constituents that can be applied in intentional drugs (Table 15.13). The same works among the conventional herbal medicines and newer methods of navel DDS—i.e., nanotechnology has appointed the noteworthy therapies to the pharmaceutical in close futurity that will increase society health. It is anticipated that the effectual and valuable relevance of the natural products and herbal medicines being used with the nanocarrier will increase the importance of available DDSs.

8. Toxicity issues

Even though nanomedicines provide numerous options in the region of DD to diagnose and treat different illnesses, their safety should not be declined. Due to the construction of nanocarriers for the efficient transport of medicine molecules in biotechnology uses, the original critical materials faced with traditional pharmaceutical therapies such as the no

Table 15.12: Herbal nanomedicine applications in tissue engineering.

Herbal	Nanomaterials	Uses	References
Vincristine (VCR), paclitaxel (PTX), etoposide (ETP), curcumin (CUR), resveratrol, CPT, genistein, quercetin, and capsaicin (CAP)	-	Anticancer profile	[37]
PTX	Multiwalled carbon nanotubes	Good aqueous solubility, biocompatibility, and high targeting ability significant enhancement in cytotoxic capability, thus improving the antitumor activity of the drug in cancer therapy	[138]
AV	Electrospun nanofibrous scaffold using PLACL, AV, and silk Fibroin (SF) PLACL-SF scaffold containing AV	Skin regeneration through improved adhesion and proliferation of HDF cells	[139]
AV	Hydroxyapatite (HA) deposited electrospun PCL—SF—AV scaffold	Osteo regeneration through increasing the adhesion, Proliferation and differentiation of adipose-derived stem cells (ADSCs)	[140]
AV	Electrospun PLACL-AV-SF NFs scaffolds NFs PLACL-AV-SF scaffolds cell	Cardiac regeneration through improving adhesion, proliferation, and differentiation of cardiomyocytes cells obtained from rats.	[141]

exact distribution, quick permission, irrepressible release of medicines, low access, and a sharp decrease in their toxicity or ADR. In contrast to the significant expansions of the latest methodologies, nearly all nanocarrier activity is correlated with several undesirable side effects, thus diminishing their practical uses in nanomedicine.

This peaks some critical issues in the design and engineering of nanocarrier systems for biotechnology uses, gaining from the mixed surroundings and multiform actions and reactions appointed within the exceptional biological environment. The basic parameters severely impressing the design of nanostructure systems for the transfer of active medicines and chemotherapeutics should be considered. Hence, the contemporary challenges and limitations, and emerging approaches of the nanoplatforms for therapeutic applications are significant issues [145].

Table 15.13: Nano-herbal medicine using in antioxidant application.

Herbal	Nanomaterials	Uses	References
CUR	pH-sensitive NPs loaded CUR-celecoxib combination	Enhanced efficacy for mitigating ulcerative colitis	[142]
Amines, carboxylic acids, aldehydes, and ketone	Ag NPs of *Bauhinia tomentosa* Linn	Anticancer and antioxidant activity nanosuspension potential agent for cancer therapy	[143]
SLNPs thujone, pinene, camphor	Witepsol SLNPs and carnauba	A significant release percentage of phenolic compounds at the small intestine (antioxidant activity hot melt)	[47]
Flavonoids (quercetin and kaempferol)	SNEDDS formulation of Persimmon(Diospyros kaki) leaf extract	A promising method for poorly aqueous soluble drugs, including the extract of herbal medicine to achieve a significant improvement in bioavailability	[38]
Protein-polysaccharide soluble nanocomplex	β-carotene, folic acid, CUR and ergocalciferol	Increase in antioxidant activity	[144]

9. Future perspective

No doubt, the requests to use herbal-derivative materials have been increased worldwide. More than 85% of the Middle East population, Latin America, Africa, and Asia rely on traditional medicine, and herbal medicines, for their health needs. About 100 million people in the European Union and some countries as high as 90% still use traditional, complementary, or herbal medicines. Therefore, the global market has a steep upward slope. Wholesales of Chinese plant drugs overtook more than US$83 billion in 2012, whereas this cost was 20% more than the marketplace in 2011. It has been suggested that the whole market for all herbal supplements will reach more than US$115 billion by 2020, which in Asia–Pacific is the fastest and in Europe is the largest growing market. The flourishing affirmations outstandingly consider women's questions on relevance on the synthetic medicines ADR. Therefore, human resource training can be the primary reference for research development to move from raw material to crop production. It seems that both the necessity and importance of research on the herbal medicinal field are more than ever. Some medicinal plants image only the adjuvant therapy sources in the health systems, treating various diseases, preventing disease, and even maintaining health.

Contrary to the comprehensive tests, the utilization of medicinal herbs in consumer drugs, capable investigation, and recognition of acting herb combinations and their effects can

drive to find proposals of novel therapeutic interests and the nature-based productions for the following experiences soon. To acquire this target, extensive research is significant to detect the quality of rare medicines and the formulization to affirm their use in the novel nanodrug system; consequently, animal studies and clinical trials are required to use these plants' benefits. In addition, in the development of medicine from medicinal plants, among other things, a practical plan should be developed to preserve these resources.

10. Conclusion

In 25 years, about 70% of anticancer medicines have been fulfilled from natural sources, regardless of whether partial or total chemical synthesis has had a substantial role in the process of the natural components. Due to low solvability and poor bioavailability, NT offers the advantages of enhanced bioavailability, lengthening of medicine circulation time, multiplex medicine loading, and reduced toxicity. Among the world research on plant medicines, the development and strength of these natural products in DDSs at basic and clinical trial levels are ongoing. Compared with today's treatment, there is a unique requirement to expand the better systems to properly deliver these drugs at sites and in the patient's body with enough dosage. This promise provides effective medicines relieved from the side effects of pharmacological, toxic, or hypersensitivity reactions while the human body becomes stronger. Today, plant NPS or nanostructural materials are considered an updated solution in treating cancer using DDSs. Of course, this assumes provision with the appropriate formulation and biocompatibility for the type of material. Therefore, using the various evidence related to nanoresearch that can be observed around us, plant drugs enhance their strength to treat numerous chronic illnesses and health affairs. Plant remedies as compositional and suitable resources of antioxidants and constituents can produce target diets. This is where the importance of available DDSs, plant remedies, and NT-based approaches for DDSs enhancing human health on an upward slope is adequately answered.

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BIONANOTECHNOLOGY: EMERGING APPLICATIONS OF BIONANOMATERIALS

Edited by Ahmed Barhoum, Jaison Jeevanandam and Michael K. Danquah

Bionanotechnology: Emerging Applications of Bionanomaterials explores a wide range of industrial and biomedical applications of these unique, nanoscale materials. A broad variety of key bionanomaterial applications have been reviewed, which includes drug delivery, tissue engineering, wound healing, medical implants, medical diagnostics, and therapy. Other key applicational areas, such as energy harvesting and storage, water/waste treatment, papermaking, textiles, construction industry, automotive, and aerospace have also been discussed.

The book is a valuable resource for all those seeking to gain a fundamental understanding of how bionanomaterials are used in a variety of industry sectors.

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- Covers the past, present, and future of functionalized bionanomaterials technology and its emerging applications in different fields.
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- Demonstrates the cutting-edge developments in bionanomaterial technologies, which have been translated into real-world innovations in various industries.

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